ECHOCARDIOGRAPHIC EVALUATION OF CARDIAC FUNCTION IN PATIENTS WITH NEWLY DETECTED TYPE 2 DIABETESMELLITUS

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CERTIFICATE

This is to certify that this dissertation entitled "ECHOCARDIOGRAPHIC EVALUATION OF CARDIAC FUNCTION IN PATIENTS WITH NEWLY DETECTED TYPE 2 DIABETES MELLITUS " submitted by **Dr. S. SAMUTHIRAVEL,** to the Tamil Nadu Dr. M.G.R. Medical University Chennai is in partial fulfillment of the requirement for the award of M.D. DEGREE BRANCH –I (General Medicine) and is a bonafide research work carried out by him under direct supervision and guidance.

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DECLARATION

I solemnly declare that the dissertation entitled "ECHOCARDIOGRAPHIC EVALUATION OF CARDIAC FUNCTION IN PATIENTS WITH NEWLY DETECTED TYPE 2 DIABETES MELLITUS " was done by me at Stanley Medical College and Hospital during 2009-2010 under the guidance and supervision of Prof. Dr. A. GOWRISHANKAR, M.D.

The dissertation is submitted to the Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfillment of requirement for the award of M.D.DEGREE (BRANCH-I) in General Medicine.

Place : Chennai
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CONTENTS

INTRODUCTION

Diabetes mellitus which is now being termed as an epidemic is spiraling upwards at an alarming rate, raising worldwide concern about its devastating effects on health and healthcare systems. It is estimated that presently there are 200 million diabetics and it is expected to reach 360 million by 2030 as per World Health Organization projections, with the largest number of cases going to be seen in China, India and USA. More than 90% of these are likely to be type 2 diabetes (DM) individuals.

In recent years with the explosion of knowledge and the sound pathophysiological basis, the distinction between the type2 diabetes and the cardiovascular disease has been blurred, and the central importance of Cardio Vascular Disease (CVD) prevention is becoming an integral part of DM management.

T2DM carries an equivalent cardio vascular risk to that of non diabetic individual who already experienced a coronary event [(1)]. DECODE study [(2)] has shown that even before diabetes is detected, the person may be predisposed to CVD and these prediabetic levels of blood sugar predict mortality.

A substantial body of evidence supports the concept that the increase risk of morbidity and mortality due to CVD is associated with abnormalities in glucose metabolism across the entire continuum of glucose tolerance ranging from normal to clinical diabetes [(1,3)] Compared with patients without diabetes, patients with DM have a 2-4 fold greater risk of death from MI or stroke[(3)].

Diabetes mellitus is an established risk factor for congestive heart failure, but the knowledge of the pathophysiology and treatment is limited. The Framingham Heart study has shown that the incidence of congestive cardiac failure in diabetic patients occurs irrespective of coronary artery disease or hypertension [(3)].

In overt heart failure, diastolic dysfunction often co-exists with systolic dysfunction as a consequence of ischemic heart disease, but diastolic dysfunction is a frequent finding in type 2 diabetes mellitus without signs and symptoms of heart disease and is presumably due to diabetic cardiomyopathy. Left ventricular diastolic function (LVDF) is affected earlier than systolic function in the development of congestive cardiac failure [(4)].

Therefore left ventricular diastolic dysfunction may represent the first stage of diabetic cardiomyopathy, thus an early examination of left ventricular diastolic function may help to detect this condition in patients with diabetes, thereby allowing early intervention for a more favorable outcome[(5)].

This study was done to understand the burden of left ventricular diastolic dysfunction (LVDD) in patients with newly diagnosed type 2 diabetes and to assess the risk factors for the development of diastolic dysfunction in such patients.

AIM OF THE STUDY

- To assess the effect of isolated type 2 diabetes on left ventricular systolic and diastolic functional reserve.

- To assess the risk factor associated with heart failure in diabetic patients.

- To compare this prevalence to that of age and sex matched asymptomatic control population.

REVIEW OF LITERATURE

Diabetes Mellitus refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Several distinct types of DM exist and are caused by a complex interaction of genetics and environmental factors.

HISTORY

The first documented evidence of diabetes mellitus was reported in Egyptian papyrus, as a polyuric state. In 1776 Mathew Dobson established the presence of sugar in blood and urine of diabetic patients. Type 2 diabetes is the commonest form of diabetes in any country.

EPIDEMIOLOGY

The global evidence of diabetes is estimated to increase from 4% in 1995 to 5.4% by the year 2025. Considerable geographic variation is seen, with most of the cases from India, USA, and Europe. India has the dubious distinction of having the highest number of diabetes in the world.The prevalence in India varies from 1.7 to 9.6% in various studies. A multicenter study done by India Council of Medical Research showed a prevalence rate of 1.73 percent in Indians above 15 yrs of age. According to Prevalence Of Diabetes in India Study(PODIs) the prevalence of type 2 diabetes in India is urban-9.6% rural-4.2% .

AETIOLOGY OF DIABETES MELLITUS

Type I diabetes mellitus

1. Genetics:

Genetic predisposition is possible permissive and not casual. Risk of diabetes is up to 5 times higher when the father is diabetic rather than mother. This risk is limited to father carrying an HLA DR4 susceptibility gene.

Risks for identical twin is 33%. Genetic loci - Chromosome 6

2. Viruses

20% of persons with congenital rubella develop IDDM. Cytomegalovirus is present in genome of 20% patients. Others implicated are Coxsackie, Mumps and hepatitis.

3. Diet

Introduction of cow's milk before the age of 2 – 3 months is associated with an increased risk.

4. Pancreatic pathology

Insulitis

TYPE II DIABETES MELLITUS

Genetics :

Probably polygenic

The role of genetic factors in the etiology of type 2 DM has been appreciated ever since the recognition of the disease. There is almost 100% concordance in monozygotic twins. Maturity onset diabetes may be associated with a mutation of glucokinase gene.

Life style

Over eating; especially combined with obesity and under activity, leads to diabetes mellitus.

Age

It is principally a disease of middle aged and elderly

Pregnancy

80% of women with gestational diabetes develop permanent diabetes requiring treatment later in life.

Insulin resistance

There is increased hepatic glucose production and resistance to the action of insulin in muscle.

ETIOLOGIC CLASSIFICATION OF DIABETES MELLITUS

1. Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)

A. Immune – mediated
B. Idiopathic

2. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)

3. Other specific types of diabetes

A. Genetic defects of β-cell function characterized by mutations in:

a. Hepatocyte nuclear transcription factor (HNF) 4 α (MODY 1)
b. Glucokinase (MODY 2)
c. HNF – 1 α (MODY 3)

d. Insulin promoter factor (IPF) 1 (MODY 4)

e. HNF – 1 β (MODY 5)

f. Mitochondrial DNA

g. Proinsulin or insulin conversion

B. Genetic defects in insulin action

a. Type A insulin resistance

b. Leprechaunism

c. Rabson – Mendenhall syndrome

d. Lipoartrophic diabetes

C. Disease of the exocrine pancreas – pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy.

D. Endocrinopathies – acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma.

E. Drug or chemical induced – Vacor, pentamidine, nicotinic acid,glucocorticoids, thyroid hormone, diazoxide, β-adrenergic agonists, thiazides,phenytoin, α- interferon, protease inhibitors, clozapine, and beta-blockers.

F. Infections – congenital rubella, cytomegalovirus, Coxsackie

G. Uncommon forms of immune mediated diabetes –
"stiff-man" syndrome, antiinsulin receptor antibodies.

H. Other genetic syndromes sometimes associated with diabetes – Down's syndrome, Klinefelter's syndrome, Turner's syndrome, Wolfram's syndrome, Friedreich's ataxia, Huntington chorea, Laurence – Moon –Biedl syndrome, myotonic dystrophy, porphyria, Prader-Willi syndrome.

4. Gestational diabetes mellitus (GDM).

RISK FACTORS FOR TYPE 2 DIABETES MELLITUS

a. Family history of diabetes (i.e. parent or sibling with type 2 diabetes)
b. Obesity (i.e. > 20% desired body weight or BMI > 25 kg/m2)
c. Age > 45 years
d. Race/ethnicity (e.g. African, American, Hispanic American, Native American, Asian American, Pacific Islander)
e. Previously identified IFG or IGT
f. History of GDM or delivery of baby over 9 pounds.
g. Hypertension (blood pressure > 140/90 mm Hg)
h. HDL cholesterol level < 0.90 mmol/L (35 mg/dL) and / or a triglyceride level 2.82 mmol/L (250 mg/dL)
i. Polycystic ovary syndrome

STAGES OF DIABETES

Stages of diabetes range from normal glucose tolerance, through IGT and IFG (impaired fasting glucose), into frank diabetes mellitus, which may be non-insulin requiring, insulin requiring for control and insulin requiring for survival.

Type 1 DM can be found across the whole spectrum. In the early stages of treatment there can be a period of non-insulin requirement, but later followed by insulin requirement for survival. In type 2 DM, insulin may be required during a period of ketoacidosis precipitated by severe stress or infection.

Diabetes and heart

Patients with diabetes mellitus are at increased risk for cardiovascular diseases. Thus, cardiovascular complications are the leading cause of diabetes-related morbidity and mortality[(2)].

The American Heart Association recently designed DM as a major risk factor for cardiovascular disease (same category as smoking hypertension and hyperlipidaemia). Type 2 diabetic patient without a prior M1 have a similar risk for coronary artery related events as non-diabetic individuals who have had a prior myocardial infarction[(3)].

The main factor that contribute to the increased incidence of cardiovascular disease in diabetic patients are

1. The acceleration of atherosclerotic process leading to macrovascular disease.
2. Development of specific cardiomyopathy.
3. Progressive microvascular disease.
4. Development of autonomic neuropathy.

Heart failure

Heart failure is a complex clinical syndrome manifesting as the inability of the heart to fill with or eject blood due to any structural or functional cardiac conditions. Heart failure can be broadly classified into Systolic Heart Failure or Heart Failure With Reduced Ejection Fraction (HFREF) and Heart Failure with Normal Ejection Fraction (HFNEF) also earlier known as Diastolic Heart Failure. There can also be a combination of both.

Systolic heart failure

Heart failure caused by systolic dysfunction is more readily recognized. It can be described as impaired contractile or pump function of the heart. It is characterized by a decreased ejection fraction (less than 45%). The strength of ventricular contraction is attenuated and inadequate for creating an adequate stroke volume, resulting in inadequate cardiac output. In general, this is caused by dysfunction or destruction of cardiac myocytes or their molecular components.

Diastolic heart failure

Diastolic heart failure, is defined as symptoms of heart failure in a patient with preserved left ventricular function. It is characterized by a stiff left ventricle with decreased compliance and impaired relaxation, which leads to increased end diastolic pressure. Signs and symptoms are similar to those of heart failure with systolic dysfunction.

Pathophysiology of diastolic heart failure [7]

Diastole is the process by which the heart returns to its relaxed state; it is also the time for cardiac perfusion. During diastole, drastic changes in cardiac pressure-volume relationships occur. The relaxation process has four identifiable phases: isovolumetric relaxation from the time of aortic valve closure to mitral valve opening; early rapid filling after mitral valve opening;

diastasis, a period of low flow during mid-diastole; and late filling of the ventricles from atrial contraction (Figure 1).

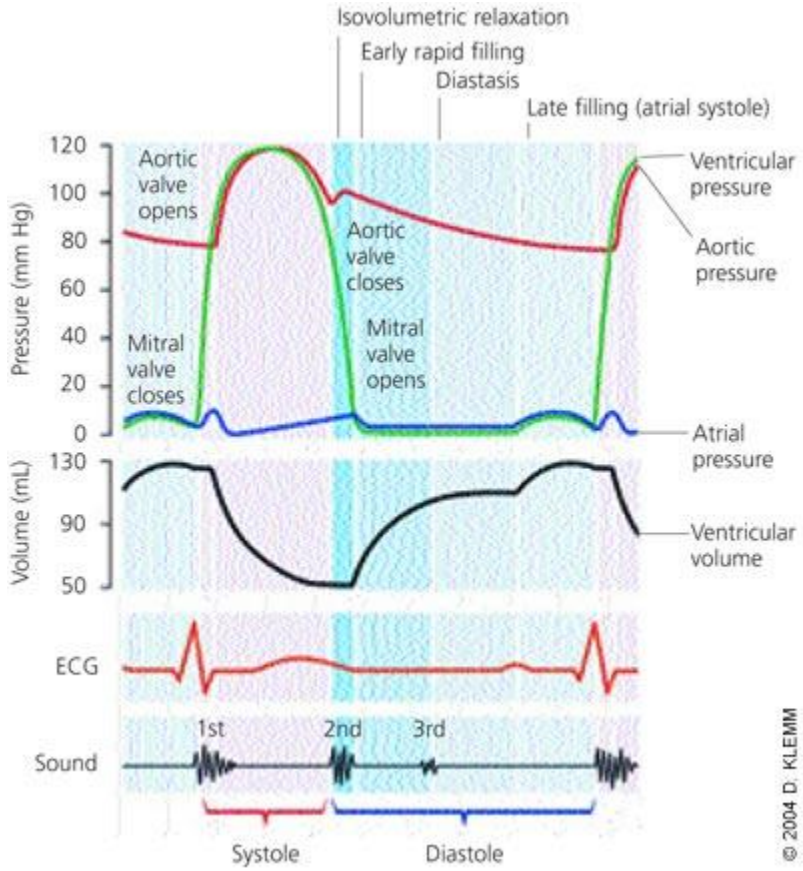


Figure 1.Cardiac cycle, showing changes in left atrial pressure, left ventricular pressure, aortic pressure, and ventricular volume; the electrocardiogram (ECG); and the phonocardiogram.

In patients with isolated diastolic heart failure, the heart often is able to meet the body's metabolic needs, but at higher diastolic pressures. The left ventricle is stiff, with decreased compliance and impaired relaxation. Transmission of the higher end-diastolic left ventricular pressure to the pulmonary circulation may lead to pulmonary congestion, dyspnea, and other symptoms of heart failure.

Diastole is a complex process that is affected by a number of factors, including ischemia, heart rate, velocity of relaxation, cardiac compliance (i.e., elastic recoil and stiffness), hypertrophy, and segmental wall coordination of the heart muscle

Heart failure in diabetes

Diabetes accounted for a significant percentage of patients with a diagnosis of heart failure in numerous epidemiologic studies. The Framingham Study,[3] United Kingdom Prospective Diabetes Study,[8] Cardiovascular Health Study, and Euro Heart Failure Surveys all suggested that the presence of diabetes may independently increase the risk of developing incident heart failure.

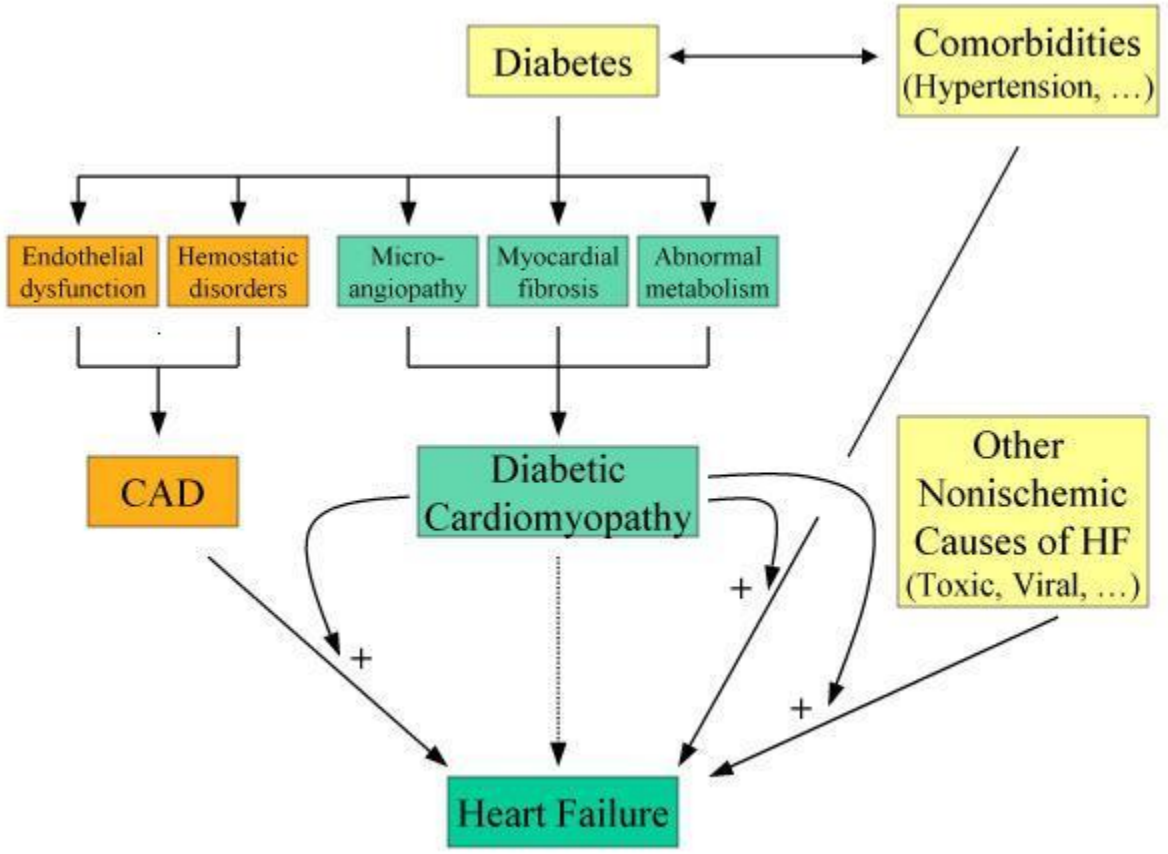
The etiology of this abnormality is probably multi factorial and includes factors such as myocardial ischaemia from atherosclerosis, hypertension and myocardial dysfunction secondary to chronic hyperglycemia.

The mechanisms of HF in diabetic patients

Figure 3 illustrates the varies mechanism of heart failure in diabetes mellitus. DM may be causally related to HF development by at least 3 mechanisms:

1. Due to associated comorbidities,
2. By favoring the development of coronary atherosclerosis,
3. Through a specific diabetic cardiomyopathy.

Figure. 2 Potential mechanisms linking diabetes mellitus to heart failure.



Potential mechanisms linking diabetes mellitus to heart failure: Diabetes mellitus is associated with multiple physiopathological changes in the cardiovascular system. Among these, endothelial dysfunction and hemostatic disorders may at least in part account for the higher risk of coronary artery disease (CAD) while microangiopathy, myocardial fibrosis, and abnormal myocardial metabolism have been implicated in the pathogenesis of a specific diabetic cardiomyopathy.

When it occurs in diabetic patients, heart failure (HF) is, in most cases, a consequence of CAD; other possible causes include the comorbidities frequently encountered in diabetic patients such as hypertension, or other causes of nonischemic cardiomyopathy. The existence of a diabetic cardiomyopathy may increase the risk of HF in response to these insults; however, whether diabetic cardiomyopathy alone may be responsible for HF remains unknown.

Diabetic cardiomyopathy

Diabetic cardiomyopathy has been defined as the presence of myocardial abnormalities in the absence of coronary artery disease, hypertension or other significant etiology[3]. Hyperglycemia seems to be central to the pathogenesis of diabetic cardiomyopathy and to trigger a series of maladaptive stimuli that result in myocardial fibrosis and collagen deposition. These processes are thought to be responsible for altered myocardial relaxation characteristics and manifest as diastolic dysfunction on imaging [9].

Pathogenesis of Diabetic Cardiomyopathy:

Mechanisms[10]

The pathogenesis of diabetic cardiomyopathy is multifactorial. Several hypotheses have been proposed, including autonomic dysfunction, metabolic derangements, abnormalities in ion homeostasis, alteration in structural proteins, and interstitial fibrosis[11,12] Sustained hyperglycemia also may increase glycation of interstitial proteins such as collagen, Interstitial accumulation of advanced-glycated end products (AGEs), which results in myocardial stiffness and impaired contractility[13–15]

Several mechanisms that are involved in decreasing myocardial contractility in diabetes mellitus. These are

(1) Impaired calcium homeostasis,

(2) Upregulation of the renin-angiotensin system,

(3) Increased oxidative stress,

(4) Altered substrate metabolism, and

(5) Mitochondrial dysfunction.

Impaired calcium homeostasis

The mechanisms by which disturbed calcium homeostasis alters cardiac function in diabetes include reduced activity of ATPases,[16] decreased ability of the SR to take up calcium, and reduced activities of other exchangers such as Na^+-Ca^{2+} and the sarcolemmal Ca^{2+}ATPase.[17,18] Furthermore, decreased cardiac expression of SERCA2a or the Na^+Ca^{2+} - exchanger has been observed in type 1[10] and type 2 diabetes.[20] Trost et al[21] observed that transgenic mice overexpressing SERCA2a were protected from streptozotocin-induced cardiac dysfunction, suggesting that altered calcium handling contributes to impaired cardiac function in diabetes mellitus.

Activation of the Renin-Angiotensin System

The role of activation of the renin-angiotensin system in the development of diabetic cardiomyopathy is well recognized.[22] Angiotensin II receptor density and mRNA expression are elevated in the diabetic heart.[23–25] Activation of the renin-angiotensin system during diabetes mellitus has been shown to be associated with increased oxidative damage and cardiomyocyte and endothelial cell apoptosis and necrosis in diabetic hearts, [26] which contributes to the increased interstitial fibrosis.

Increased Oxidative Stress

Increased reactive oxygen species (ROS) production in the diabetic heart is a contributing factor in the development and the progression of diabetic cardiomyopathy[27,28] Several groups have shown that ROS is overproduced in both type 1 and type 2 diabetes.[29,30] Increased ROS generation may activate maladaptive signaling pathways, which may lead to cell death, which could contribute to the pathogenesis of diabetic cardiomyopathy.[31] Thus, increased ROS-

mediated cell death could promote abnormal cardiac remodeling, which ultimately may contribute to the characteristic morphological and functional abnormalities that are associated with diabetic cardiomyopathy.

In addition to causing cellular injury, increased ROS production might lead to cardiac dysfunction via other mechanisms. For example, increased ROS has been proposed to amplify hyperglycemia-induced activation of protein kinase C isoforms, increased formation of glucose-derived advanced glycation end products, and increased glucose flux through the aldose reductase pathways,[32,33] which may all contribute in various ways to the development of cardiac complications in diabetes mellitus. Thus, strategies that either reduce ROS or augment myocardial antioxidant defense mechanisms might have therapeutic efficacy in improving myocardial function in diabetes mellitus.

Altered Substrate Metabolism

Altered myocardial substrate and energy metabolism has emerged as an important contributor to the development of diabetic cardiomyopathy.[34,35]. Diabetes mellitus is characterized by reduced glucose and lactate metabolism and enhanced fatty acid (FA) metabolism.[36,37] Despite an increase in FA use in diabetic hearts, it is likely that FA uptake exceeds oxidation rates in the heart, thereby resulting in lipid accumulation in the myocardium that may promote lipotoxicity[(38-40)]. Lipid intermediates such as ceramide might promote apoptosis of cardiomyocytes, thus representing another mechanism that might lead to cardiac dysfunction.[41]

Free Fatty Acid Metabolism Disturbances

Figure 3 summarizes the role of altered free fatty acid metabolism and its contribution to the development of diabetic cardiomyopathy. Figure 4 illustrates the role of hyperglycemia in

inducing the ultimate downstream effects. In the absence of diabetes, approximately equivalent proportions of energy required for cardiac contractility come from glucose metabolism and free fatty acids; whereas in diabetes, myocardial glucose use is significantly reduced, with a shift in energy production from beta-oxidation of free fatty acids.[42] This reduction in glucose use in the diabetic myocardium results from depleted glucose transporter proteins, glucose transporter-1 and 4. In addition, free fatty acids inhibit pyruvate dehydrogenase, which impairs myocardial energyproduction and leads to the accumulation of glycolytic intermediates and ceramide, enhancing apoptosis.[43,44] In addition to the effects of free fatty acids on glucose metabolism and oxidative phosphorylation, free fatty acid metabolism for adenosine triphosphate production requires large amounts of oxygen. The toxic intermediates resulting from free fatty acid metabolism[(42,45)] (so-called lipotoxicity) can impair myocyte calcium handling, worsening myocardial mechanics.[46-48]

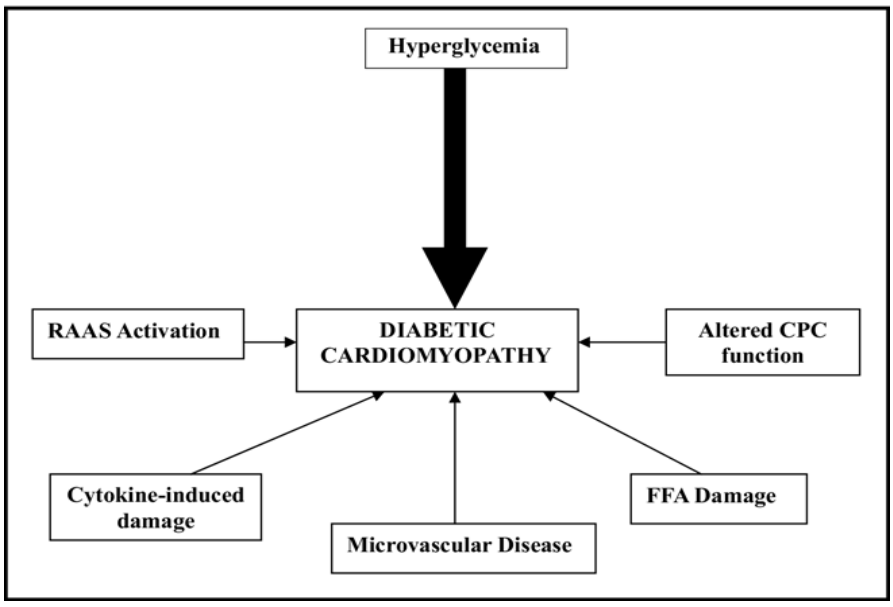


Figure 3 Overall schema for the pathogenesis of diabetic cardiomyopathy.

FFA-free fatty acid; CPC-cardiac progenitor cells; RAAS-renin-angiotensin-aldosterone system

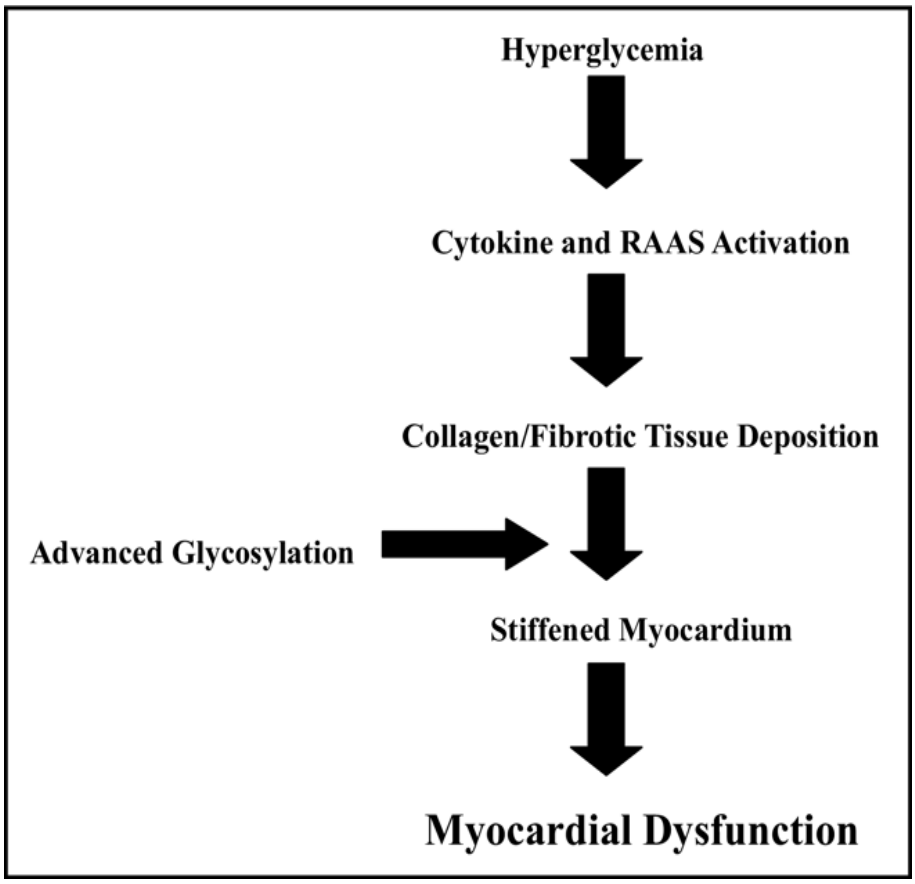


Figure 4 Effects of hyperglycemia on the diabetic myocardium.

Mitochondrial Dysfunction

Recent studies of mitochondria have reignited interest in a role for mitochondrial dysfunction in the pathogenesis of diabetic cardiomyopathy.[49-51] Diabetes mellitus causes functional and structural alterations in mitochondria.

Impaired mitochondrial function was initially reported almost 25 years ago when Kuo et al showed depressed state 3 respiration in db/db heart mitochondria. This study was followed by others showing reduced mitochondrial oxidative capacity in type 1 diabetes.[52–55]

Boudina et al demonstrated decreased mitochondrial respiration and reduced protein expression of the oxidative phosphorylation components in obese type 2 diabetic mice.[49] These alterations contribute to cardiac dysfunction because they reduce ATP production, which we speculate will diminish myocardial high-energy phosphate reserves, thereby contributing to impaired myocardial contractility.

Autonomic Neuropathy

Diabetic autonomic neuropathy can lead to changes in sympathetic innervations and subsequent disordered adrenergic receptor expression and altered catecholamine levels in the myocardium. An increased expression of theβ1-receptor results in enhanced apoptosis, fibrosis, hypertrophy, and impaired myocardial function.[56]

DIAGNOSING DIABETIC CARDIOMYOPATHY

There are 2 important components in the clinical diagnosis of diabetic cardiomyopathy: the detection of myocardial abnormalities and the exclusion of other contributory causes of cardiomyopathy.

An important challenge in the clinical diagnosis of diabetic cardiomyopathy has been the lack of any pathognomonic histologic changes or imaging characteristics associated with the diagnosis. Endomyocardial biopsies are not indicated because of their invasiveness, unless circumstances to suspect other causes of cardiomyopathy in the differential diagnosis exist (eg, hypertrophic cardiomyopathy and infiltrative heart diseases).Nevertheless, the presence of myocardial fibrosis or collagen deposition can be fairly characteristic of diabetic cardiomyopathy. Electron

microscopic features, including mitochondrial abnormalities, fatty acid deposits, or even myocyte hypertrophy, can be evident.

The diagnosis of diabetic cardiomyopathy currently rests on noninvasive imaging techniques that can demonstrate myocardial dysfunction across the spectra of clinical presentation. There is still no consensus in the precise imaging definition of diabetic cardiomyopathy, but evidence of hypertrophy or diastolic dysfunction is likely crucial to support a diagnosis of diabetic cardiomyopathy, but is not specific to it.

On the basis of the review of the literature, the imaging definition of diabetic cardiomyopathy that includes either or both features listed as follows:

● Evidence of cardiac hypertrophy determined by conventional echocardiography or cardiac magnetic resonance imaging;

● Evidence of LV diastolic dysfunction (with or without LV systolic dysfunction), either clinically by transmitral Doppler or tissue Doppler imaging (TDI), or evidence of left atrial enlargement; or subclinically by novel imaging techniques or provocative testing (eg, strain rate imaging or stress imaging).

Methods of diagnosing diastolic dysfunction

Cardiac catheterisation with simultaneous pressure and volume measurements is the "gold standard" for assessing LV diastolic function. The rate of LV relaxation, rate and timing of diastolic filling as well as myocardial and chamber stiffness can be determined [57]. However, this diagnostic method is invasive and cannot be performed in all patients with suspected diastolic dysfunction.

During the last two decades, Doppler echocardiography has emerged as an important and easy to perform noninvasive diagnostic tool providing reliable data on diastolic performance. The trans-mitral flow across the mitral valve demonstrates a biphasic pattern, in which an early peak flow occurs during rapid early diastolic filling (peak E) and a late peak occurs during atrial contraction (peak A).Based on Doppler trans mitral flow, a grading system for diastolic dysfunction has been proposed.

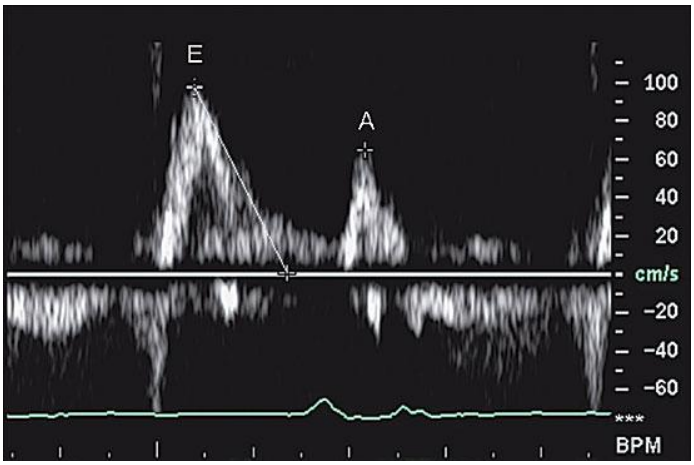
Three characteristic abnormal LV diastolic filling patterns mainly based on the E/A ratio have been proposed [58]

- The first abnormal filling pattern, called "delayed relaxation", results in a reversed E/A ratio (E/A < 1) when relaxation impairs. It identifies patients with early stages of heart disease.
- The second pattern, representing abnormalities of both relaxation and compliance, has been termed pseudo normalization, because of an apparently normal E/A ratio (E/A > 1). This results from an increase in left atrial pressure compensating for slow relaxation.

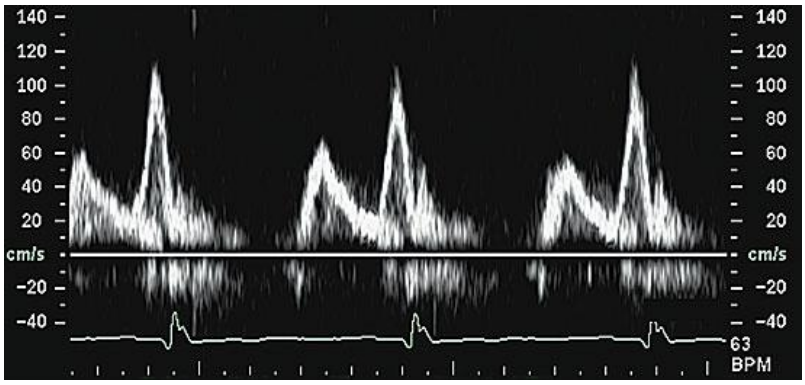
- The third abnormal filling pattern, termed “restrictive filling”, found in patients with severe decrease in LV com pliance, causes an increased E/A ratio (often above 2). It identifies advanced, usually symptomatic disease with poor prognosis.

Other Doppler derived indices have been proposed, of which deceleration time (the time interval of peak E wave velocity to zero), and isovolumic relaxation time (time from the end of systolic ventricular outflow to mitral valve opening) are applied most often.

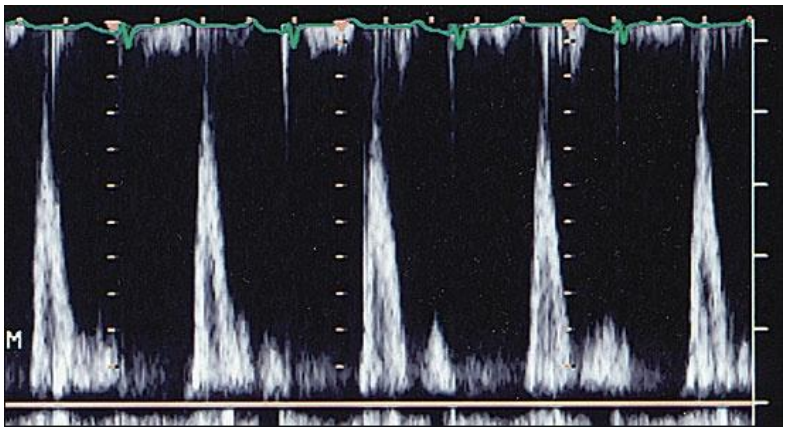
Figure 2. Schematic drawing of mitral inflow patterns during different stages of diastolic dysfunction. E= early inflow wave; A= atrial contraction, A wave.



Normal trans–mitral-valve spectral Doppler flow pattern. The E-to-A-wave ratio is pproximately 1.4 to 1.0.



Trans–mitral-valve Doppler flow tracing in a patient with mild diastolic dysfunction (abnormal relaxation). The E-to-A-wave ratio is less than 1.0.



Trans–mitral-valve Doppler flow pattern in a patient with severe (restrictive) diastolic dysfunction. The E-to-A-wave ratio is abnormally high, and the A-wave velocity is extremely low.

LEFT VENTRICULAR FUNCTION IN DIABETES MELLITUS

Numerous studies have shown that impairment of the LV diastolic function may be detected in patients with diabetes The existence of a diabetic cardiomyopathy was first suggested by Rubler et al [(59)] in 1972 on the basis of postmortem findings in four adult diabetic subjects with non-coronary congestive cardiac failure (CCF)

.

Subsequent observations by the Framingham workers about the most frequent occurrence of CCF among the diabetics than could be explained by hypertension or ischemic heart disease alone, interest was renewed in the field of cardiac involvement in long-standing diabetic patients.

Regan *et al.* [60] demonstrated in normotensive, diabetic patients without coronary artery disease and without clinical evidence of heart failure, increased left-ventricular end-diastolic pressure,a decreased left-ventricular end-diastolic volume with a normal ejection fraction

Hamby et al [(61)] Impaired left ventricular (LV) function may frequently be detected in asymptomatic diabetic subjects and is related to the extent of diabetes and evidence of micro vascular complications. Although systolic and diastolic functions of the heart are impaired in diabetes, many studies have shown that the LV diastolic abnormalities are most common and may in fact precede the development, of systolic abnormality.

Thus, diastolic abnormalities present in diabetic patients without diabetic complications or cardiovascular disease has been suggested as an earliest functional effect of a specific diabetic cardiomyopathy [62, 63].

In the large majority of studies, abnormalities of LVdiastolic function have been demonstrated in diabetic patients with intact systolic function Raev *et al.* [64].

It is now clear from the various studies that the primary functional abnormality in a diabetic heart is the impairment of LV diastolic function reflecting the reduced LV filling and that even the systolic functional alteration is the result of reduced LV filling.

EVALUATION OF LV FUNCTION IN DIABETIC SUBJECTS

There are two chief methods of evaluating the LV function

1. Utilizing the non-invasive techniques.
2. Invasive techniques

Non-invasive methods include the assessment by

a) Systolic time intervals (STI)

b) Apex cardio graphy (ACG)

c) Radio nucleotide ventriculography

d) Echocardiography and cardiac Doppler

Invasive method is by cardiac catheterization delineating the coronary artery anatomy and LV angiography. This procedure is usually reserved for symptomatic diabetic subjects with overt or those who manifest CCF and is unnecessary in asymptomatic although long-standing diabetics.

ECHOCARDIOGRAPHY- M-MODE AND 2-D

Aerakisnen et al(65) utilizing the digitalized M-mode technique studied 36 female IDDM patients with a mean duration of diabetes of 10 years or more and found that the most common abnormality (19 pts) was prolonged rapid filling period while the systolic function was normal in all. Another study recorded simultaneous echo and phonocardiogram in142diabetics. The LV relaxation, the rate and duration of cavity dimension increase and wall thinning were determined. Delayed mitral valve opening (MVO) relative to minimal LV cavity dimension and aortic valve closure (AVC) was found in all but 12 subjects, especially in those with micro vascular complications. Prolongation of isovolumic relaxation time (IVRT) i.e. measured as period between AVC and MVO (abnormal, if more than 110 m sec), which can be demonstrated using dual M-mode echo preferably at 100 min/sec speed showing simultaneous aortic and mitral valve levels, is an important diastolic abnormality, as found by Sanderson et al[(66)] .

Others using quantitative cross-sectional echocardiography and stress myocardial perfusion scintigraphy found that diabetic subjects had mildly reduced LV end diastolic volumes and impaired diastolic filling as assessed by lower left atrial emptying index compared to controls. The left atrial emptying index is defined on M-mode tracing of the aorta

DOPPLER TECHNIQUES

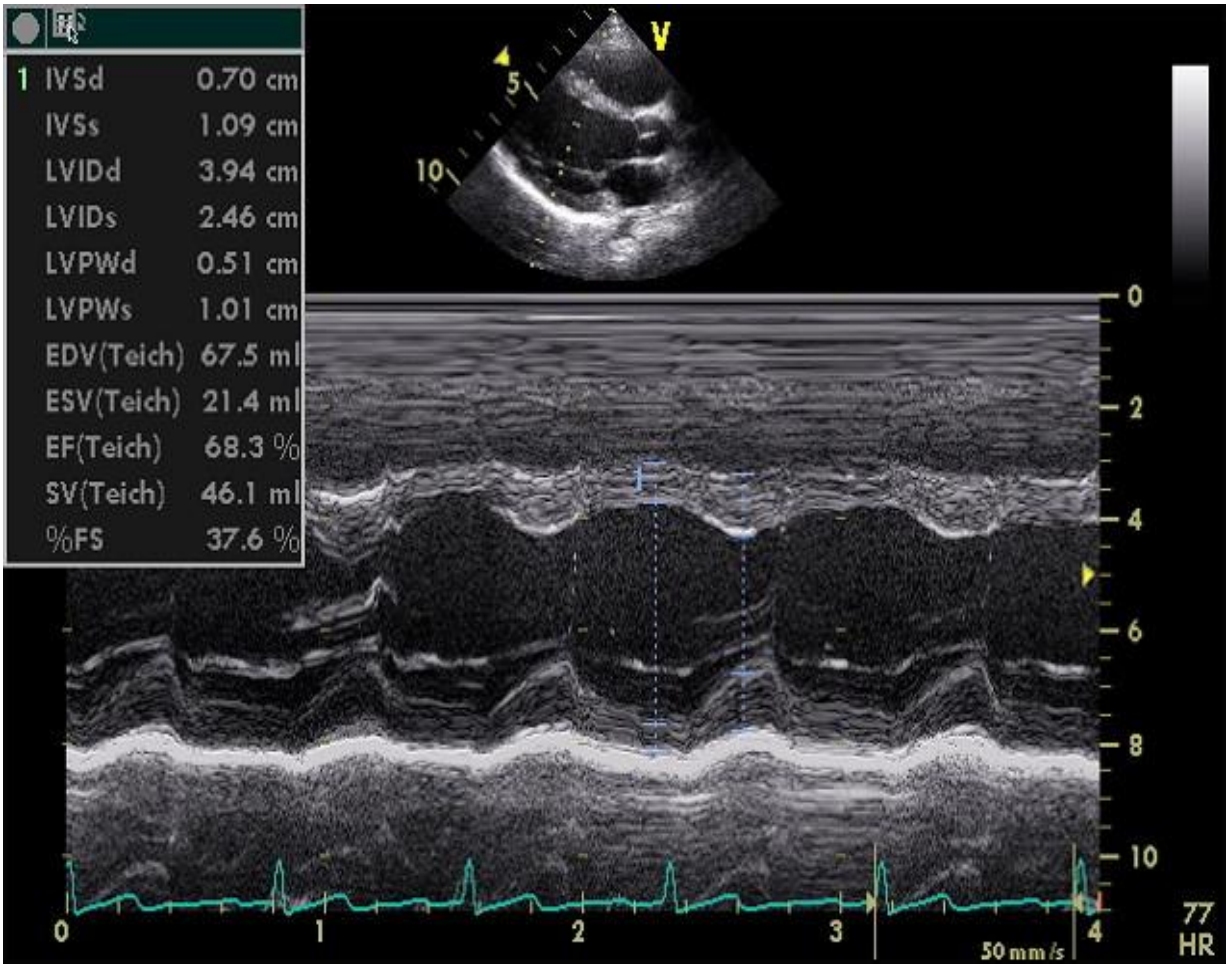
Pulsed Doppler ultrasound interrogation of mitral inflow velocities (Doppler cursor placed at the tips of the mitral leaflets on apical 4-chamber view) gives a simple and reproducible method of determining the LV filling that correlates well with radio nucleotide and invasive techniques. Ventricular filling in the normal subjects is characterized by a biphasic pattern with an initial

peak velocity of rapid early ventricular filling ('E') and a relatively low peak velocity of late inflow due to atrial contraction (A). Impaired diastolic filling of the left ventricle in both Type 1 and Type 2 asymptomatic diabetics without the evidence of cardiovascular disease and unrelated to microangiopathic complications has been demonstrated using PW Doppler which showed reduction in the early filling velocity (reduced 'E' peak) and compensatory increase in the late flow (increased 'A' peak) and thus increased A/E ratio (i.e. A/E more than 1). Besides, the deceleration of 'E' velocity is prolonged indicating a slow rapid-filling phase ('E' deceleration more than 250 m/sec). Increased atrial contribution to LV filling can be assessed by the area under the late diastolic filling envelope compared to the total diastolic area. Various studies have demonstrated these above Doppler findings in young diabetic subjects without evidence of heart failure.

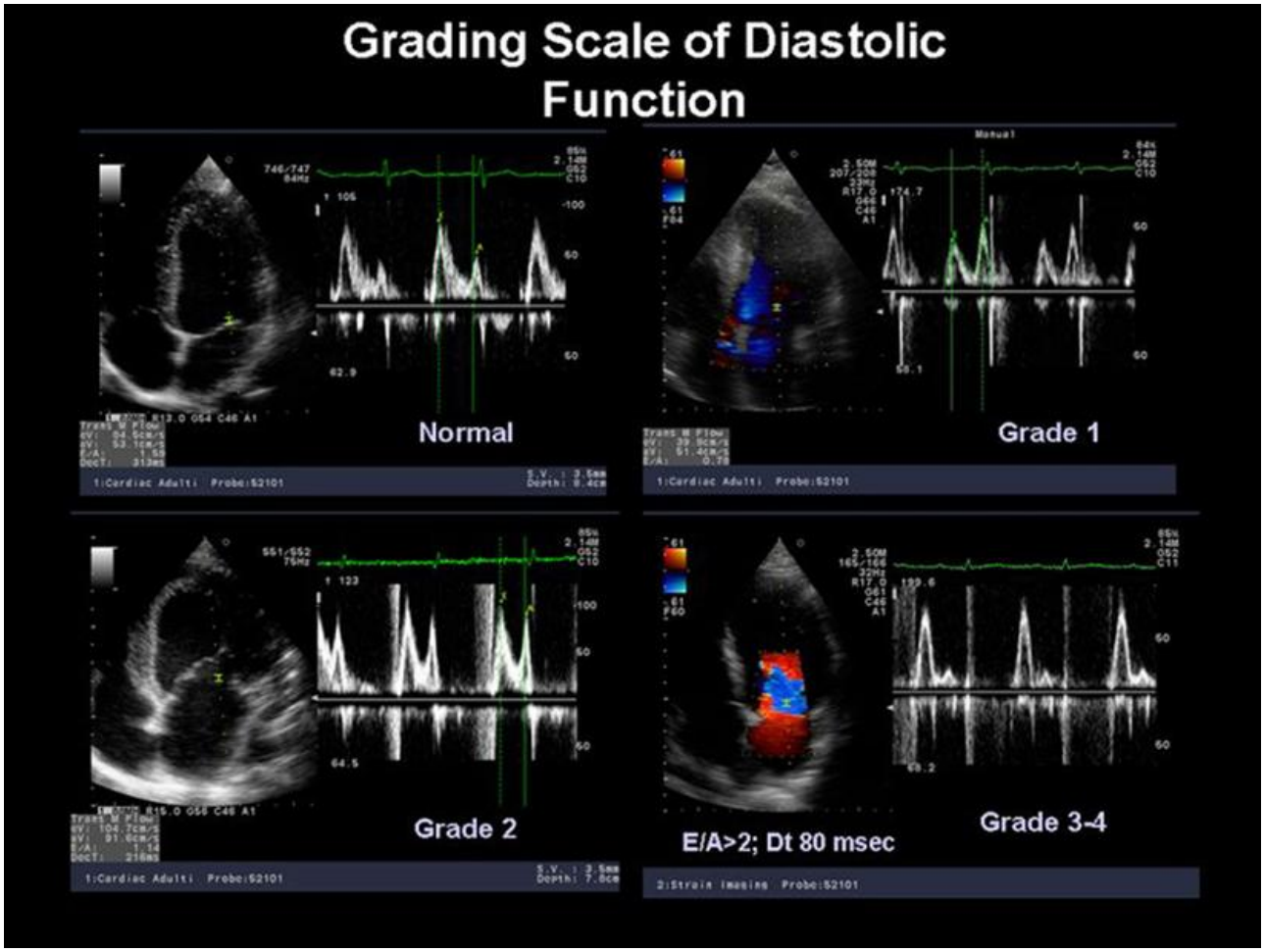
A 3-year follow-up study by Charella et al of a group of asymptomatic diabetics with slow filling and wall thinning demonstrable on echocardiography showed 31% developing heart failure and 19% that died. Measurement of LV diastolic function may therefore prove to be a useful indicator of cardiovascular morbidity and mortality in diabetics.

Hence abnormal diastolic function suggestive of reduced LV compliance resulting in a 'Stiff' myocardium appears to be the hall mark of the specific type of diabetic heart muscle disease. The presence or addition of hypertension or coronary artery disease will certainly put a new burden on the already 'non-compliant' myocardium in long-standing diabetics with or without micro vascular complications**.**

ECHO PICTURE OF M-MODE SHOWING VARIOUS LV DIMENSIONS



DOPPLER ECHO SHOWING GRADING OF DIASTOLIC DYSFUNCTION



PREVENTION AND THERAPY

Glycemic Control

The prevention and treatment of diabetic cardiomyopathy are clinically relevant because of its role in the pathogenesis of heart failure. Although the effect of glycemic control on diabetic cardiomyopathy has been studied in only a limited fashion, evidence suggests that good glycemic control is beneficial, at least in the early stages of myocardial dysfunction [(67-69)]. Evidence also suggests that diabetic cardiomyopathy does not develop in patients with tightly controlled type 1 diabetes, supporting an important role for hyperglycemia in the pathogenesis of diabetic cardiomyopathy[70]. Hyperglycemia is responsible for microvascular complications in diabetes, and because microvascular alterations are thought to contribute significantly to the pathogenesis of diabetic cardiomyopathy, **good glycemic control** is perhaps the most important component in the overall management of diabetic cardiomyopathy. Firm recommendations regarding the choice of current glucose-lowering therapies in patients with diabetic cardiomyopathy cannot be made because of a lack of evidence.

However, **glucagon-like peptide-1 analogues** have demonstrated improved hemodynamic variables in diabetic patients without overt heart failure. Improved cardiac parameters also have been noted with this agent class in post infarction and in populations with advanced heart failure[(71)]. On the other hand, the use of thiazolidinediones in the management of patients with diabetic cardiomyopathy is problematic because of a propensity for fluid overload. In general, the choice of antidiabetic therapy in diabetic cardiomyopathy should be dictated by clinical characteristics,such as the presence or absence renal dysfunction, risk of hypoglycemia, age, volume status, and concomitant drug therapy.

Neurohormonal Antagonism

The important role of the renin-angiotensin-aldosterone system in the pathogenesis of complications in diabetic patients is well described. Evidence supports the use of **Angiotensin-Converting Enzyme Inhibitors** in preventing myocardial fibrosis, cardiac hypertrophy, and myocardial mechanical dysfunction associated with diabetic cardiomyopathy.[72-74] Angiotensin-converting enzyme inhibition and angiotensin-1 receptor blockade also have been shown to prevent coronary perivascular fibrosis and collagen deposition.[75] The **Angiotensin Receptor Blocker**, candesartan, can improve echocardiographic parameters of diastolic dysfunction, reduce collagen synthesis, and increase collagen degradation in asymptomatic diabetic subjects.[76]

Novel Therapies Targeting Diabetic Cardiomyopathy

Therapies directed toward the prevention and progression of diabetic cardiomyopathy are in the early stages of clinical development and have targeted either enhanced fibrosis/collagen deposition or alterations in cardiomyocyte metabolism.The majority of the agents listed below are in experimental stages, and none of them have been approved for use in diabetic cardiomyopathy. Notable among these novel agents are **Advance Glycation End Product Inhibitors** (eg,aminoguanidine, alanine aminotransferase 946, and pyridoxamine);**Advance Glycation End Product Cross-Link Breakers** (eg, alanine aminotransferase 711); and copper chelation therapy (eg, trientine). **Modulators of free fatty acid metabolism**,such as trimetazidine, have proven useful in the management of angina, but their efficacy on diabetic cardiomyopathy is unknown. **Exenatide** (recombinant glucagon-like peptide-1, a Food and Drug Administration-approved glucose-lowering agent) has yet to be studied specifically in patients with diabetic cardiomyopathy patients despite promising cardiac effects with glucagon-like peptide-1 infusion in mechanistic studies.

MATERIALS AND METHODS

The Clinical materials were newly diagnosed Type-2 Diabetes Mellitus individuals selected from Diabetic outpatient department and the department of internal medicine in the Stanley hospital,Chennai-1

About 77 patients were subjected to initial assessment , it included through clinical examination, routine blood investigation consisting of biochemistry investigation, ECG, estimation of HbA1c and echo cardiography were done from which 50 patients were included in the study and compared with 50 healthy age and sex matched controls.

Informed consent was obtained from all the subjects and the hospital ethical board committee ethically approved the study.

The Period of study was from march 2009 to September 2010.

STUDY DESIGN – case control study

STUDY GROUPS

Group I - 50 newly diagnosed Type II Diabetes Mellitus patients.

Group II - 50 healthy controls**.**

These groups were selected on the basis of inclusion and exclusion criteria.

INCLUSION CRITERIA

- Newly diagnosed Type II Diabetes Mellitus
- Healthy controls

EXCLUSION CRITERIA

- Patients with age above 70
- Systemic Hypertension.
- conduction disturbance on ECG.
- Documented Ischaemic heart disease
- History suggestive of previous angina, congestive cardiac failure.
- Documented evidence of other cardiac disease like cardiomyopathy
- Valvular heart disease
- Congenital Heart Disease
- primary myocardial diseases,
- pericardial diseases,
- Chronic obstructive pulmonary disease
- sustained arrhythmias
- CKD
- liver diseases
- thyroid diseases
- pregnancy and seriously ill patients

New cases were diagnosed by the revised criteria for diagnosis of diabetes mellitus.

CRITERIA FOR DIAGNOSIS

Revised criteria for diagnosing diabetes mellitus has been issued and taken from American Diabetes Association and the World Health Organization.

The criteria is based on the premises that

1. The spectrum of fasting plasma glucose (FPG) and the response to an oral glucose load varies in normal individuals.

2. Diabetes Mellitus defined as the level of glycemia at which diabetic specific complications are noted and not on the level of glucose tolerance from a population based viewpoint.

CRITERIA for Diagnosis of Diabetes[(6)]

1. HgbA1c of ≥ 6.5% is new diagnostic criterion. Needs to be done in a lab setting using NGSP certified method and following DCCT standard (point of care tests are not accepted)
2. HgbA1C can not be used to diagnose diabetes in pregnancy nor in patients with anemia from iron deficiency or hemolysis Increased rate of red cell turnover
3. Fasting Plasma Glucose > or = 126 (no calories for 8 hours)
4. 2 hour plasma glucose > or = 200mg/dl using 75gm OGTT
5. Random plasma glucose > or = 200 with hyperglycemia Symptoms

Note: In the absence of unequivocal hyperglycemia and acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day.

All of them were subjected to echocardiography done at the Department of Cardiology, Stanley hospital, Chennai. Echocardiograms were done using the commercially available Esaote`S My Lab50. which has the capabilities of performing two dimensional, M mode, Pulsed wave and continuous wave Doppler and colour flow imaging was used to obtain echo cardiogram images. Phased array transducers 2.5 - 3.5 MHz frequencies were used to obtain 2-D / M-mode echo cardiography. Images were obtained with subjects in 30 degree lateral decubitus position. All measurements were performed in the freezed images from all the patients, good quality images suitable for the measurements and interpretations were obtained and recorded.

For assessment of LV systolic function the following parameters were calculated from the M-mode echocardiogram obtained at the level of mitral valve chordae. LV dimension diastole (LVId) systole (LVsd) and thickness of inter ventricular septum, left ventricular posterior wall thickness in diastole.LV ejection fraction was calculated using the following formula,

EF= LVEDV-LDESV/ LVEDV x 100

For the assessment of LV diastolic dysfunction following parameters were calculated from doppler transmitral flow velocities in the apical 4-chamber view by positioning the pulsed doppler sample volume between the tips of the mitral leaflets.

1. LV filling during the early rapid phase(E wave m/s),
2. LV filling during atrial contraction (A wave m/s)
3. Ratio of the filling velocity E/A ratio
4. Deceleration time (from the peak of E wave to the point at which the deceleration velocity reaches the base line)
5. Isovolumetric relaxation time. (from the aortic valve closure to the beginning of E wave)

STATISTICAL ANALYSIS

All data were expressed as mean ± SD. Statistical analysis was performed using Graph pad Instat. Student`s T test were used between group comparison. Differences in variables between patients with and without LV diastolic dysfunction were analyzed using Fisher's Exact test and a P value of less than 0.05 was considered as statistically significant.

OBSERVATIONS AND RESULTS

OBSERVATIONS

Table No 1. SEX DISTRIBUTION

Category	Sex		Total
	Female	Male	
Diabetic patients	32	18	50
Controls	30	20	50

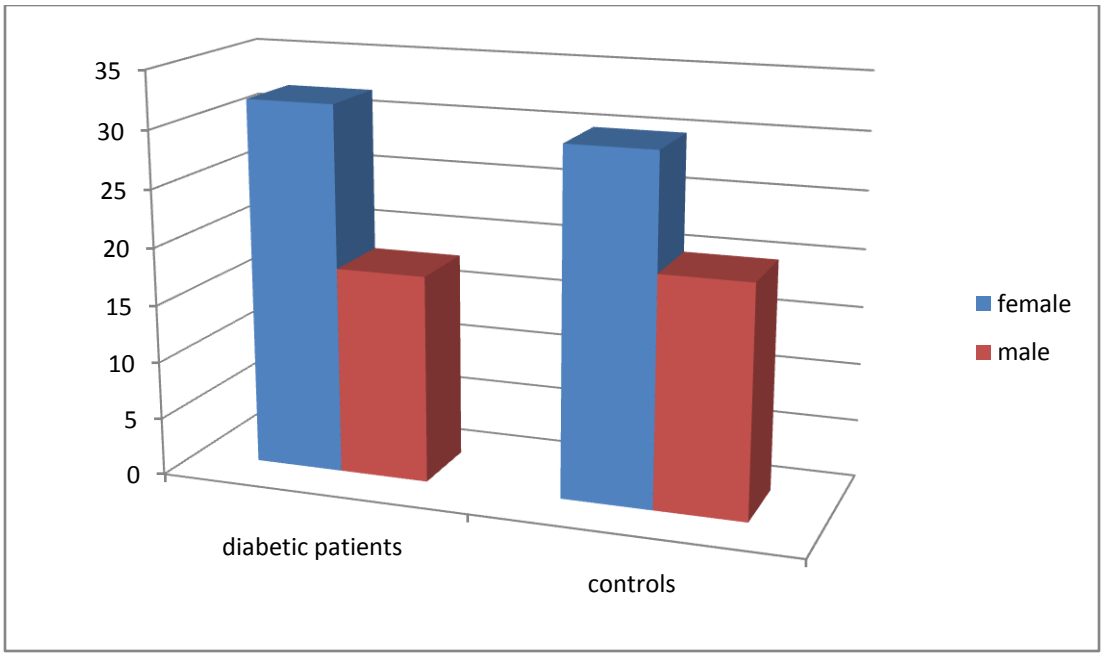
Out of 50 patients in study group, 32 were female and 18 were male. In control group 30 were female and 20 were male.

Table No. 2 AGE DISTRIBUTION

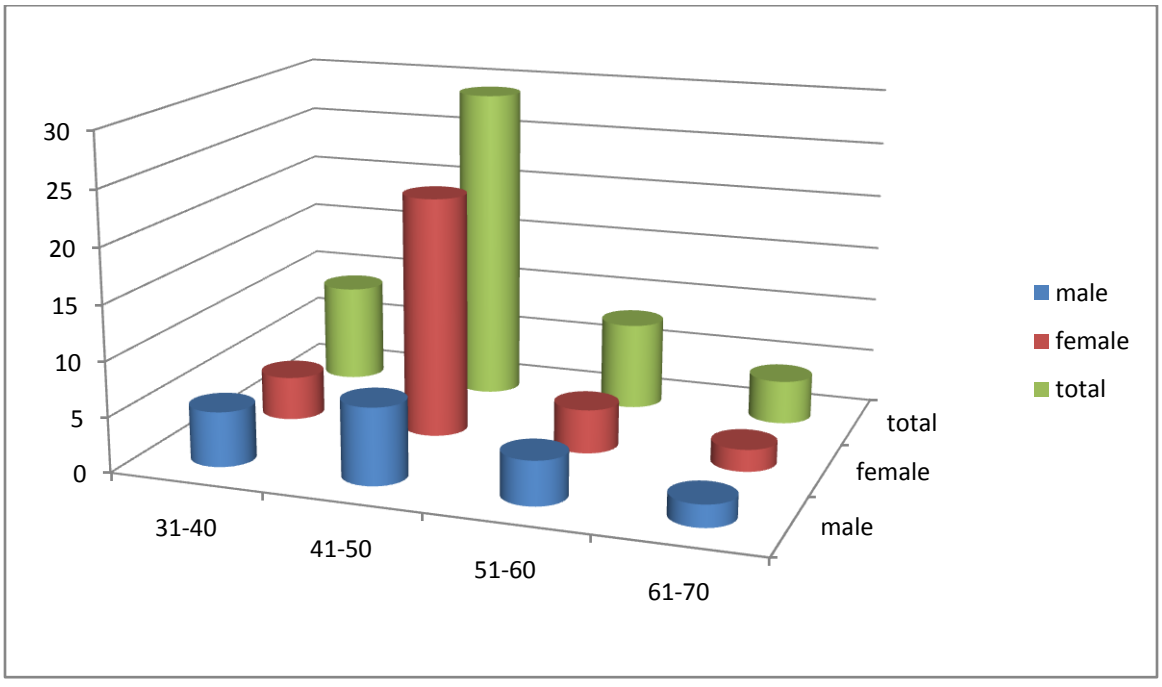
Age(in Years)	Control group				Diabetic group			
	Male	Female	Total	%	Male	Female	Total	%
31-40	4	4	8	16%	5	4	9	18%
41-50	8	21	29	58%	7	22	29	58%
51-60	5	3	8	16%	4	4	8	16%
61-70	3	2	5	10%	2	2	4	8%

More than half of the study population and control population belong to age group of 41-50 years (58%).

SEX DISTRIBUTION



AGE DISTRIBUTION IN DIABETIC PATIENTS



OBESITY ASSESSMENT

The Health Ministry has reduced the diagnostic cut-offs for body mass index (BMI) to 23 kg/m2 and the standard waist circumference to assess obesity [77]

Table No .3 DISTRIBUTION OF BMI IN DIABETIC GROUP

Body Mass Index		**31-40 years**	**41-50 years**	**51-60 years**	**60-70 years**	**Total**	**Percentage**
<18.5	Low BMI	0	1	1	0	2	4%
18.6-23	healthy	6	7	2	1	16	32%
23.1-25	Over wt	4	7	2	1	14	28%
>25	obesity	0	13	3	2	18	36%

In study groups 4% were in low BMI

32% were in healthy state

28% were overweight and

36% were obese .

Table No.4 DISTRIBUTION OF BMI IN CONTROL GROUP

Body mass index		31-40 years	41-50 years	51-60 years	60-70 years	Total	Percentage
<18.5	Low BMI	2	3	1	1	7	14%
18.6-23	healthy	9	8	3	3	23	46%
23.1-25	Over wt	4	8	1	2	15	30%
>25	obesity	1	2	2	0	5	10%

14% had low BMI, 46% had acceptable BMI, 30% had over weight and 10% had obesity

In this study, obesity is more in diabetic population than control groups (36% vs.10%)

- Unfavorable BMI was found in 32 patients out of 50(64%) 18 were overweight and 14 were obese in diabetic group, where as in control group 20 people had un favorable BMI (40%) 15 were overweight and 5 were obese.

Table No.5 Distribution of Waist Hip Ratio in study and control groups

Waist hip ratio	Male			Female		
	≤0.95 low risk	**0.96-1 moderate risk**	**1.0+ high risk**	**≤0.80 low risk**	**0.81-0.85 moderate risk**	**0.85+ high risk**
No of diabetic patients	8	4	6	4	8	20
controls	14	3	3	12	9	7

In study group 52% were in high risk. Females (40%) are more in high risk than male(12%).

In control groups 20% were in high risk. Here also females (14%) are more in high risk than male(6%) .

STATISTICAL ANALYSIS

STUDY GROUP	BMI mean value	T value	P value
Total DM patients Total control	25.396 ± 4.375 22.012 ± 3.441	4.298	**<0.0001**
Male patients Male control	24.846 ± 4.949 22.669 ± 4.116	1.480	0.1477
Female patients Female control	25.872 ± 4.089 23.187 ± 3.948	2.657	**0.010**

STUDY GROUP	W/H ratio	T value	P value
DM patients control	0.9226 ± 0.1252 0.8372 ± 0.0919	3.887	**0.0002**
Male patients Male control	0.9389 ± 0.1369 0.8570 ± 0.1155	1.999	0.0532
Female patients Female control	0.9134 ± 0.1148 0.8332 ± 0.0768	3.353	**0.0013**

Lipid analysis

Study group	S.cholesterol	T value	P value
Patients	205.08 ± 31.04	4.190	<0.0001
control	178.90 ± 31.43		

Study group	TGL	T value	P value
patients	197.18±74.93	4.611	<0.0001
control	142 ± 38.46		

Study group	HDL	T value	P value
patients	42.4±8.827	2.349	0.0208
control	46.44 ± 8.367		

Study group	LDL	T value	P value
patients	124.26±32.47	4.289	<0.0001
control	97.51 ± 29.82		

The above statistical analysis showed significant correlation between groups regarding the Body Mass Index, Waist/Hip Ratio, Triglycerides, total cholesterol, HDL, and LDL.

Table .6 COMPARISON OF CHARACTERISTICS BETWEEN SUBJECTS WITH NORMAL AND THOSE WITH DIASTOLIC DYSFUNCTION IN DIABETIC POPULATION

Variables	Diabetic patients		T value	P value
	With Normal LV function(36)	with diastolic dysfunction(14)		
Age years	45.56 ± 7.16	53.07 ± 8.76	3.129	**0.003**
Male :female	14:25	4:10		
BMI	24.48 ± 3.96	27.18 ± 3.64	2.205	**0.0323**
W/H ratio	0.907 ± 0.13	0.963 ± 0.11	1.437	0.1585
FBS	163.28 ± 44.41	187.5 ± 56.49	1.603	0.1156
PPBS	261.81 ± 61.74	316.86 ± 57.86	2.879	**0.0059**
HBA1C	8.13 ± 1.48	9.16 ± 1.4	2.250	0.0291
T.CHOLESTEROL	197.75 ± 25.52	223.93 ± 36.72	2.868	0.0061
TGL	179.17 ± 56.53	243.5 ± 97.03	2.927	**0.0052**
HDL	43.97 ±8.5	38.36 ± 8.65	2.088	0.0422
LDL	117.81 ± 26.9	140.86 ± 40.20	2.356	0.0226
Urea	30.87±7.7	33.77±9.6	0.9740	0.3350
S.Creatinine	0.74±3.8	0.79±4.3	0.7645	0.2643
ECHO variables				
IVS thickness	10.36 ± 1.53	11.61 ± 0.99	2.806	0.0072
LVPW thickness	9.26 ± 1.18	10.75 ± 1.2	3.973	**0.0002**
EF%	57±8.2%	58±6.8%	0.762	0.2613

Baseline characteristics and laboratory data shows significant differences within diabetic group regarding the Body Mass Index, Waist/Hip Ratio, FBS, PPBS, Triglycerides, total cholesterol, HDL, and LDL. No significant differences with respect to urea and creatinine concentrations were observed.

Echocardiographic data are showed there were no significant differences within diabetic group regarding left ventricle ejection fraction, but there were significant differences in thickness of interventricular septum, thickness of left ventricle posterior wall.

Table No .7 TRANSMITRAL DOPPLER FLOW VELOCITY RECORDING

Doppler parameter	**Diabetic patients**		**control**	
	Subjects with normal cardiac function	**Subject with diastolic dysfunction**	**Subjects with normal cardiac function**	**Subject with diastolic dysfunction**
Number	36(72%)	14(28%)	45(90%)	5(10%)
E wave(cm/s)	71± 10	56 ±10	69± 11	58 ± 12
A wave(cm/s)	58 ±8	71 ±3	52 ±9	69 ± 4
E/A	1.26± 0.09	0.78 ±0.053	1.34± 0.17	0.81 ± 0.10
DT(ms)	218 ± 46	244 ±51	189 ± 42	238 ± 48
IVRT(ms)	106±19	110 ±11	90±17	109 ± 12

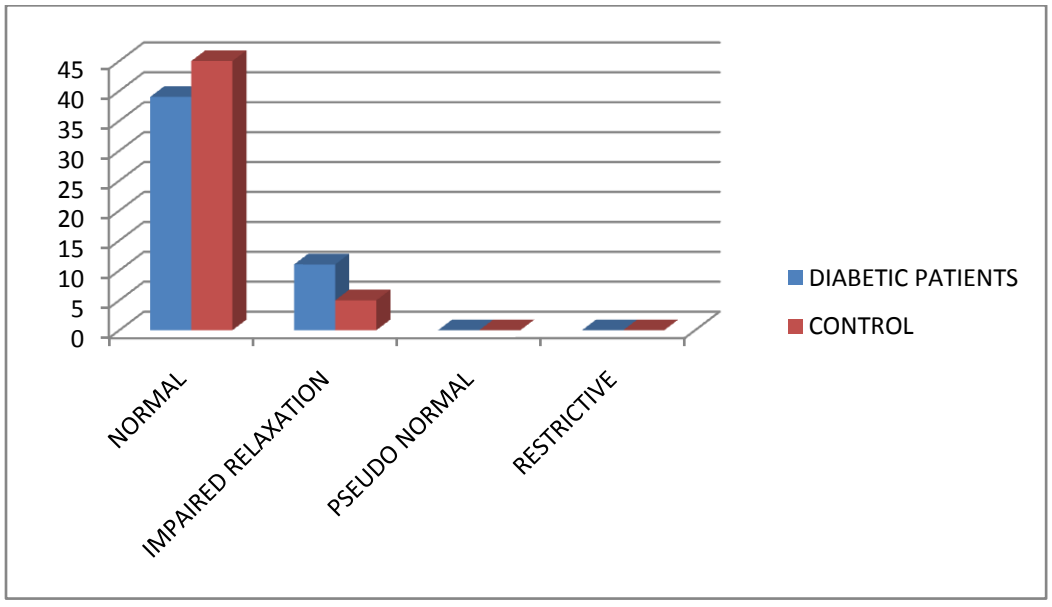
Transmitral velocity data showed the significant low E/A ratio (E<A), prolonged declaration time (>240ms) and isovolumetric relaxation time (>110ms) in patients with diastolic dysfunction both in study group and control group.

Table .8 GRADING OF DIASTOLIC DYSFUNCTION IN STUDY GROUPS

Diastolic function category	New diabetic patients	Control group
1.Normal pattern	36	45
2.Impaired relaxation	14	5
3.Pseudo normal pattern	0	0
4.Restrictive pattern	0	0

All of them had Grade I Diastolic dysfunction only**.**

GRADING OF DIASTOLIC DYSFUNCTION IN STUDY GROUPS



RESULTS

Table No.9 INCIDENCE OF DIASTOLIC DYSFUNCTION IN STUDY GROUPS

Study group	With diastolic dysfunction	Without diastolic dysfunction	Total
New diabetic patients	14	36	50
control	5	45	50

Fisher`s exact test showed, the two- sided **P value is 0.0395**, and the **Relative risk is 2.80** considered statistically significant.

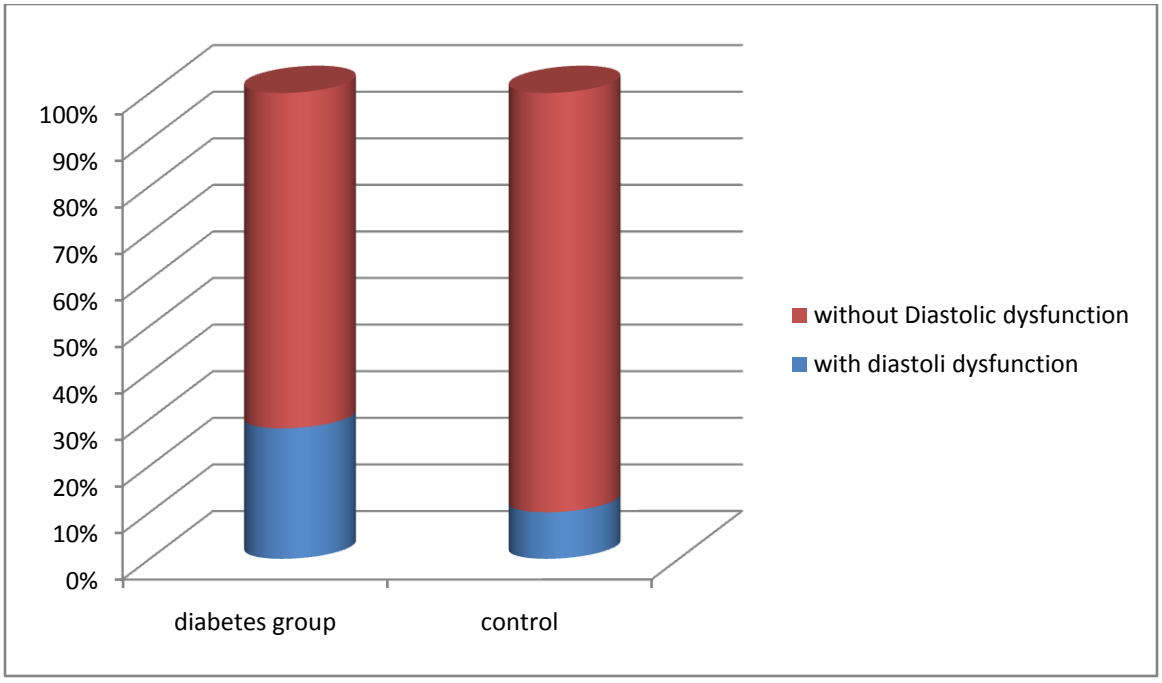
Of the 50 patients of diabetic group that were included in the study, diastolic dysfunction was detected in 14 patients giving an incidence of **28%** .Where as in control group, out of 50 people 5 had diastolic dysfunction giving an incidence of **10%** , revealing a threefold risk in the incidence of diastolic dysfunction in newly diagnosed diabetic patients.

Table No .10 DIASTOLIC DYSFUNCTION AND AGE DISTRIBUTION IN STUDY GROUPS

Age	Diastolic dysfunction	
	New diabetic patients	Control group
40-50	7	0
51-60	4	2
61-70	3	3

Diastolic dysfunction occurs more earlier in new diabetic patients than control population 50% in the age group of 40-50 years.

INCIDENCE OF DIASTOLIC DYSFUNCTION IN STUDY GROUPS



DIASTOLIC DYSFUNCTION AND AGE DISTRIBUTION IN STUDY GROUPS

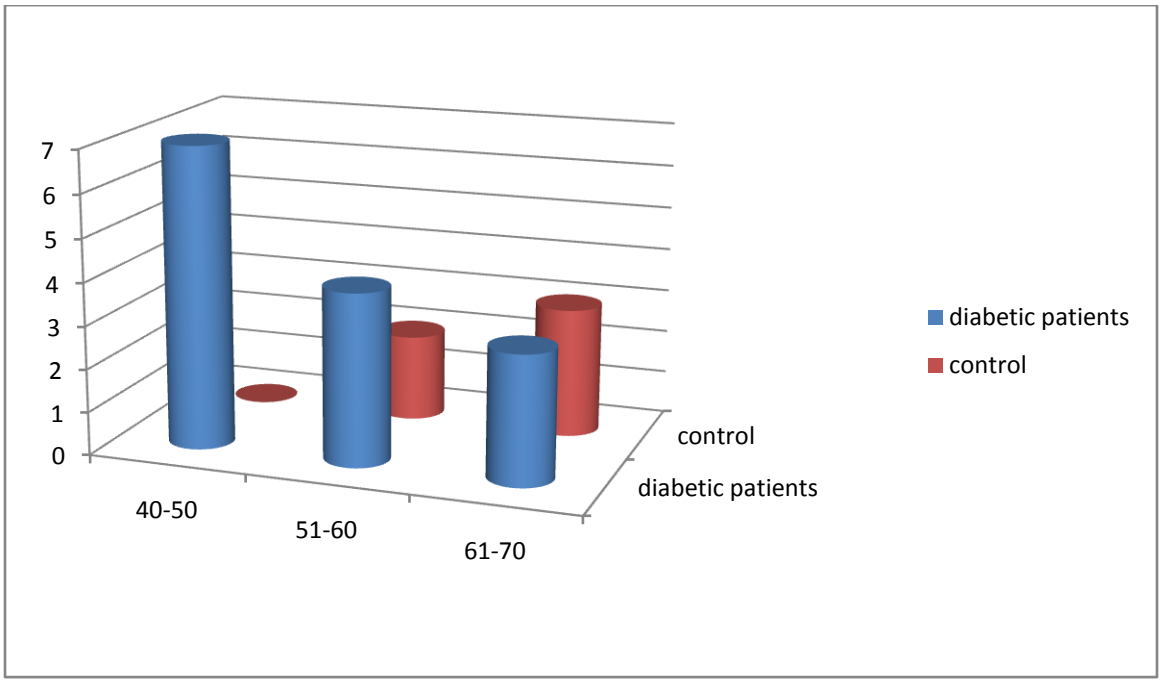


Table No. 11 GENDER DISTRIBUTION OF DIASTOLIC DYSFUNCTION

study group	diabetic patients		control group	
	normal function	with diastolic dysfunction	normal function	with diastolic dysfunction
male	14	4	18	2
female	22	10	27	3

In study groups, of the 32 **females** 10 patients**(31.25%)** had LVDD while of the 18 **males** 4 patients had LVDD**(22%).**In control groups, of the 30 females 3 person(10%) had LVDD while of the 20 males 2 person had LVDD(10%)

GENDER DISTRIBUTION OF DD IN STUDY GROUPS

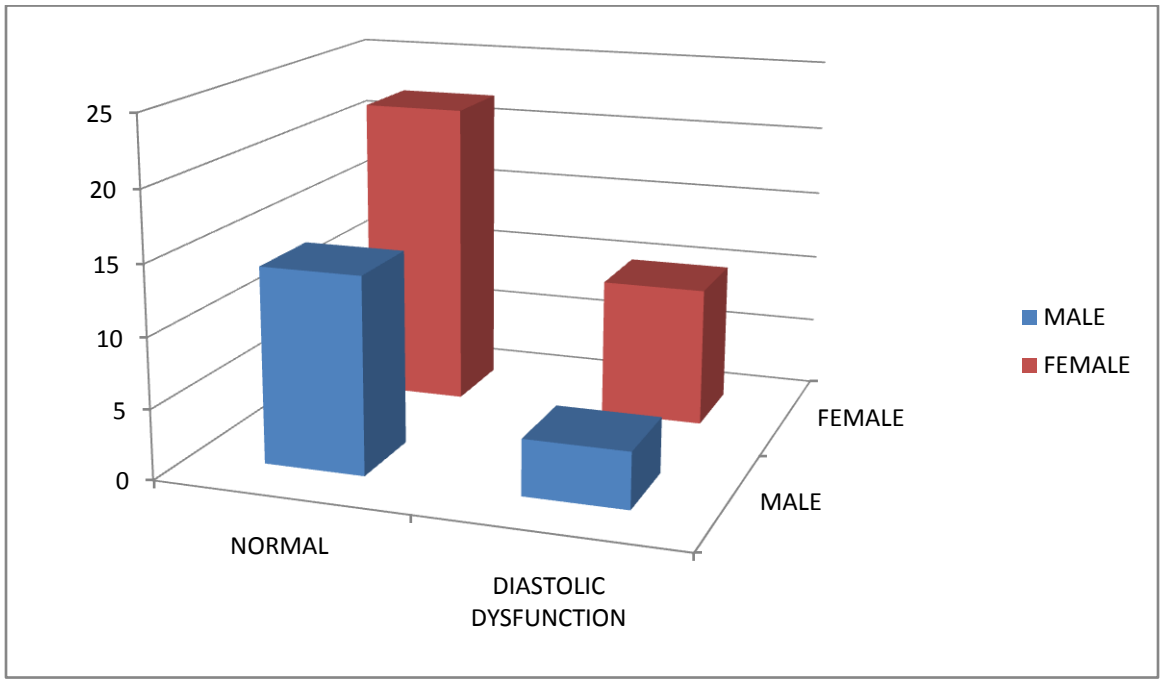


Table .12 ANALYSIS OF ASSOCIATED RISK FACTORS IN NEW DIABETIC PATIENTS WITH DIASTOLIC DYSFUNCTION

Total	BMI>25	WHR >1/>.85	FBS>200	PPBS>300	HbA_1C > 9	T. chol > 240	TGL >200	HDL <40	LDL >30
14	8	7	5	9	6	4	8	8	5

Out of 14 patients, 4 were male and 10 of them were female. 73% were obese, 64 % had higher waist-hip ratio, 45.46% had FBS >200, 82% had post prandial glucose >300 mg%, 57% had HbA_1C > 9% and >50% had dyslipidemia.

Table .13 ANALYSIS OF ASSOCIATED RISK FACTORS IN CONTROL GROUP WITH DIASTOLIC DYSFUNCTION

Total	BMI>25	WHR >1/>.85	T. Chol> 240	TGL >200	HDL <40	LDL >30
5	1	3	0	1	2	1

Out of 5 patients, 2 were male and 3 of them were female.

Compared to the patients with diastolic dysfunction in control group, new diabetic patients with diastolic dysfunction had significantly higher BMI and dyslipidemia.

In new diabetic patient, those who are having high PPBS at the time of diagnosis had significant correlation with diastolic dysfunction (P value 0.0059) .

DISCUSSION

Epidemiological data indicate a greater risk of cardiovascular morbidity and mortality, particularly congestive cardiac failure, in diabetic subjects as compared with those without diabetes [78]. The prevalence of diastolic dysfunction in diabetic population ranges from 30% to 70%.

Left ventricular diastolic dysfunction may represent the first stage of diabetic cardiomyopathy reinforcing the importance of early examination of diastolic function in individuals with diabetes.

Our study showed that the prevalence of diastolic dysfunction in newly diagnosed type 2 diabetic patients was 28% and those in control population it was 10% .

Similar findings have been reported with Doppler echocardiography (E/A ratio), in newly diagnosed type 2 diabetic patients free of microvascular complications, without evidence of hypertension and coronary artery disease [79-81].

In the study of **Gough *et al*.** [79]LVdiastolic function was assessed with pulsed wave Doppler mitral flow velocities in20 normotensive patients with a new diagnosis of type 2 diabetes mellitus. The E/A ratio was significantly reduced in the diabetic group but despite improvements in glycemic control over 3 months (HbA1c 9.9% to 7.4%), maintained at 6 months (HbA1c 7.0%), there were no changes in the E/A ratio.

In the study of **Beljic *et al*.** [80] LV diastolic function was evaluated at the onset of disease and after 6 and 12 months of adequate glycemic control. A significantly reduced value of peak E/A ratio was found in the diabetic patients before treatment, but did not significantly change after 1 year of adequate glycemic control with therapy.

Vanninen *et al.* [81] also demonstrated in a population of newly diagnosed diabetics, an improvement of diastolic function concomitantly with declining blood glucose levels evaluated after a 15-month period. Of note, this was demonstrated with a complex echocardiographic indices but not with the conventional mitral E/A ratio.

Di Bonito *et al* [82] reached to the same conclusions in a case-control study using Doppler echocardiography (E/A ratio). They observed diastolic dysfunction in 16 normotensive type 2 diabetic patients, free of microvascular complications with a disease duration of less than 1 year.

These observations of an impaired diastolic function in patients with newly diagnosed diabetes or with a short duration of the disease and with no microangiopathic complications suggest that this alteration may occur early in the history of type 2 diabetes and would not be related to microvascular complications.

Celentano *et al.* [83] studied 64 subjects with normal glucose tolerance (n = 25), with impaired glucose tolerance (n = 15) and with type 2 diabetes mellitus (n = 24) diagnosed by an oral glucose tolerance test according to the recommendations of the World Health Organization. They found early signs of diastolic dysfunction (assessed by E/A mitral flow ratio), not only in patients with diabetes but also in those with impaired glucose tolerance, independent of the confounding role of ischemia, body weight, and blood pressure.

Poirier et al(84) in 2001 in Canada attempted to determine the prevalence of left ventricular diastolic dysfunction in middle-aged asymptomatic subjects with type 2 diabetes in a study,

which included 46 men who has no evidence of diabetic complications, hypertension, coronary artery disease, congestive cardiac failure, thyroid or renal disease. Left ventricular diastolic dysfunction was found in 28 (60%) subjects impaired relaxation.

Bajraktari et al [85] in 2004 in Kosovo demonstrated that left ventricular diastolic dysfunction was present in 68.8% of asymptomatic type 2 diabetic patients as compared to 34.9% in the control group without diabetes which was due to the presence of asymptomatic diabetic cardiomyopathy which was present in the diabetic population.

It was also noted that diastolic dysfunction is more common among diabetic women and they also had a more advanced form of diastolic dysfunction as compared to men

In our study, 0f the 32 female patients 10 patients(31.25%) had LVDD while of the18 male 4 patients(22%) had LVDD

In Framingham study also females out numbered the males. The Strong Heart study by Devereuex and colleagues in 2000 also demonstrated that diastolic dysfunction is more prevalent in women than in men. [86,

This could be due to hormonal changes that accompany after menopause.

Risk Factors Associated with Left Ventricular Diastolic Dysfunction [87, 88]

Hypertension and IHD are recognized as important risk factors for left ventricular (LV) diastolic dysfunction. Some studies have shown that diabetes itself may also be an independent risk factor for LV diastolic dysfunction.

In our study post prandial blood sugar (PPBS) and HbA1c significantly correlated with diastolic dysfunction

Poirier and colleagues [84] also did not find any difference in the glycemic indices and concluded that fasting blood glucose levels did not correlate with the presence of diastolic dysfunction in type 2 diabetes. However, Holzmann and colleagues demonstrated that the presence of diastolic dysfunction is related to the concentrations of fasting blood glucose, post prandial blood glucose and HbA1c [(89)].

BMI was higher in patients with DD (27.18 ± 3.64 vs. 24.48 ± 3.96 kg/m^2; *P* value of 0.0323) , it has direct correlation with LVDD. But WHR (waist hip ratio) not significantly correlate with diastolic dysfunction

Diabetic patients who had abnormal lipid values had increased incidence of LVDD than who had normal lipid values, particularly total cholesterol and TGL with significant P value of 0.0052.

The potential risk factors for the development of diastolic dysfunction in type 2 diabetics that were determined were; (a) age ≥45 years was associated with an almost three times higher risk for the development of diastolic dysfunction, (b) females had almost two times a higher risk for the development of diastolic dysfunction as compared with men, and (c) diabetic patients with high PPBS and high HbAIc were higher risk of developing diastolic dysfunction (d)diabetic patients with high BMI and dyslipidemia was associated with higher risk for the development of diastolic dysfunction

STUDY LIMITATION

The limitation of our study was that TMT was not performed thus the possibility of coronary artery disease could not be completely excluded however the absence of clinical, Electrocardiographic and Echocardiographic evidence makes it unlikely, and this study was done in a small population.

SUMMARY

- Incidence of diabetes is more common in the age group of 41-50years
- Incidence of diastolic dysfunction is higher in new type 2 diabetic patients than control group, (28% vs 10%) with significant p value 0.039, they are in three fold risk in developing DD than general population.
- Systolic dysfunction was not found in any newly detected type 2 diabetic patients.
- Patients with LV diastolic dysfunction were older than patients without LV diastolic dysfunction in new diabetic patients.(53.07 ± 8.76 vs. 45.56 ± 7.16 years; *P 0.003*).

- Diastolic dysfunction occur more earlier in diabetic patients (40-50years), compared to control group where diastolic dysfunction commonly occur in elderly people (60-70).
- Diastolic dysfunction in new type 2 diabetic patients showed a higher incidence in female population compared to male (28% vs 22%). Interestingly diastolic dysfunction occurs in later age group in female than male (>50years vs >40 years).
- Analysis clearly showed that new diabetic patient with diastolic dysfunction had significant association with PPBS,HbA_1C, BMI and dyslipidemia.

CONCLUSIONS

- The incidence of diastolic dysfunction was found significantly high in newly diagnosed type 2 diabetes mellitus patients as compared with non diabetic subjects.
- Prevalence of diastolic diastolic dysfunction in new diabetic population has female preponderance in the ratio of 2:1 .
- Among the type 2 diabetes patients, Advancing Age, abnormal BMI, PPBS, raised HbA1c, elevated Total Cholesterol and Triglyceride were significantly associated with diastolic dysfunction.
- Hence all newly detected diabetes with these risk factors should be evaluated for cardiac function with echocardiography.
- When definite therapeutic and prevention strategies have evolved, then it may become necessary and useful to screen all new diabetic patients for LV diastolic dysfunction with echocardiography.

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PROFORMA

1.Name

2.Age

3.Sex

4.Educational status

5.Occupation

6.Family income/yr

7.Address

8.Hgt in cms

9.Wgt in kg

10.BMI(kg/m2)

11.Waist-hip ratio

12.Clinical presentation

Polyuria, Polydipsia, wgt loss

13 . other history

14.Past history-SHT, CAD ,CVA, PT

15.Personal history- Alcohol, Smoking

16.Family history

17.Menstural history-pre menopausal/post menopausal

18.Diet history; veg/non veg

Frequency/duration

19.General examination; consciousness /orientation

Vitals BP: PR:

20. Systemic examination

CVS:

RS:

Abdomen;

CNS:

21.investigations

1.Urine R/E; Alb

Sugar

Deposits

2.FBS

PPBS

3.HbA1c

4.Lipid profile

5.ECG

6 Eehocardiography

LV IVS thickness/post wall thickness/LV diameter

E/A ratio

Ejection fraction

INFORMED CONSENT FORM

I agree to participate in the study titled " ECHOCARDIOGRAPHIC EVALUATION OF CARDIAC FUNCTION IN NEWLY DETECTED TYPE 2 DIABETES PATIENTS"

I confirm that I have been told in my mother tongue and have had the opportunity to ask questions

I understand that my participation is voluntary and I may refuse to participate at any time without giving any reason and without affecting my benefits

I agree not to restrict the use of any data or results that arise from this study

Name of the participant:

Signature/ thumb print:

Witness Investigator

ABBREVIATIONS

DM	Diabetes Mellitus
CVD	Cardiovascular disease
LVDF	Left ventricular diastolic function
LVDD	Left ventricular diastolic dysfunction
IDDM	Insulin dependent diabetes mellitus
MODY	Maturity onset diabetes of young
BMI	Body mass index
WHR	Waist hip ratio
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
HF	Heart failure
AGE	Advanced glycation end products
ROS	Reactive oxygen species
FA	Fatty acid
DT	Deceleration time
IVRT	Isovolumetric relaxation time
EF	Ejection fraction
LVEDV	Left ventricular end diastolic volume
LDESV	Left ventricular end systolic volume
IVS	Interventricular septum
LVPW	Left ventricular posterior wall

MASTER CHART

NEWLY DETECTED DIABETIC PATIENTS

S.N	name	age	sex	BMI	WHR	BP	FBS	PPBS	HbAIC	TC	TGL	HDL	LDL	IVS	LVPW	E/A ratio	EF%
1	RAMALINGAM	57	M	24.89	1.08	130/80	152	247	7.7	200	150	42	110	8.2	8.7	1.3	63%
2	LAKSHMI	65	F	23.8	0.84	128/86	163	370	9.6	261	280	35	191	13	11.2	0.86	60%
3	GOWRI	50	F	23.58	0.87	136/86	134	228	7.2	176	180	56	86	9.8	10.8	1.1	62%
4	SABIR ALLAH	47	M	20.06	0.82	120/78	135	248	7.2	179	175	45	94	11	12	1.1	58%
5	SHANTHI	50	F	31.2	1.01	120/82	360	480	13.4	246	387	32	156	11.8	9.6	0.74	63%
6	POWNU	56	F	24.09	0.74	132/84	133	210	7	210	207	38	130	9.8	10	1.2	68%
7	LAKSHMI	45	F	31.11	1.06	120/80	128	198	6.8	210	232	31	132	8.6	9.8	1.4	59%
8	PARIMALA	45	F	22.51	0.72	130/70	134	221	7.1	180	156	58	89	9.8	11	1.2	55%
9	ISMAIL	64	M	23.59	1.12	126/78	162	288	9.2	230	366	36	138	10.8	9.8	0.79	64%
10	PONNUTHAI	48	F	30.54	1.04	130/80	140	210	7.1	190	173	56	99	11.8	9.5	1.3	64%
11	POOMARI	45	F	31.58	1.02	110/76	201	330	9.6	210	176	42	132	12.8	9.7	1.3	63%
12	LOKESH	35	M	22.35	0.8	120/70	138	224	7.1	187	177	50	101	13	8.9	1.2	66%
13	VENDRA	57	F	26.26	0.81	110/80	140	280	8.1	230	215	33	110	12.8	11.2	0.84	58%
14	KALYANI	45	F	22.41	0.86	124/68	168	330	9.1	198	178	46	130	11.8	11	0.78	60%
15	KASTHURI	55	F	21.93	0.88	110/70	160	276	8.3	261	206	35	190	9.6	11	1.3	61%
16	RAJAMMAL	50	F	33.29	1.1	130/70	120	192	6.6	190	168	50	100	8.2	9.9	1.3	55%
17	KAMALA	70	F	24.51	1.08	140/80	146	306	8.6	223	188	25	165	10.8	11.2	0.69	68%
18	SUMATHI	37	F	22.67	0.89	120/80	200	320	9.5	186	166	50	99	10	9.8	1.2	69%
19	THAMBIAYYAN	39	M	22.26	0.98	110/68	164	246	7.9	220	184	38	124	8.2	8.5	1.3	59%
20	RAMANI	56	F	23.49	0.84	140/82	160	278	8.3	187	177	54	88	12	13	0.82	58%
21	RAJENDRAN	44	M	24.89	0.81	130/78	180	240	8.1	210	344	42	168	9.8	7.4	1.4	64%
22	SAVITHRI	48	F	23.8	0.84	126/86	180	268	8.5	210	190	46	130	10.2	8.9	0.74	59%
23	GAJALAXMI	43	F	23.58	0.87	100/70	120	250	7.4	210	176	42	132	12.6	9.2	1.2	66%
24	SAKAYAM	51	M	31.2	1.01	110/84	220	310	9.6	188	146	54	88	10.4	12	0.73	60%
25	MUNI VEL	68	M	20.76	0.82	130/78	160	310	8.7	211	219	33	125	8.8	11	1.3	64%

NEWLY DETECTED DIABETIC PATIENTS

S.N	name	age	Sex	BMI	WHR	BP	FBS	PPBS	HbAIC	TC	TGL	HDL	LDL	IVS	LVPW	E/A ratio	EF%
26	ANJALAI	40	F	20.54	0.85	120/80	320	420	13	240	210	42	146	9.9	11	1.4	55%
27	NEELA	47	F	32	0.97	124/76	280	430	12	246	212	30	180	8.4	7.7	1.3	63%
28	LAKSHMI	48	F	24.74	1.14	110/88	140	220	7.2	190	168	52	100	12.3	9.6	1.2	58%
29	PATTU	50	F	27	0.94	134/78	210	320	9.6	183	166	54	98	13.4	10	1.3	59%
30	KULANDAIRAJ	34	M	20	0.97	126/68	138	288	8.1	190	180	56	97	11.4	8.2	1.2	68%
31	PANDIDURAI	42	M	28	0.98	130/80	168	246	8	200	246	38	130	13	11	0.86	58%
32	PECHIAMMAL	34	F	24.16	1.02	120/80	126	188	6.6	175	120	25	126	10.6	10	1.3	60%
33	VIJAYA	46	F	24.5	0.9	100/70	164	268	8.2	180	146	42	100	11	9	1.3	58%
34	MEENAKSHI	38	F	24	0.86	136/84	204	320	9.5	192	150	46	116	9.8	7.1	1.1	68%
35	JOSEPH	38	M	24.16	0.79	120/80	146	248	7.7	160	120	50	82	9.6	9.2	1.4	64%
36	MUTHU	44	F	28.12	0.97	122/78	168	310	8.9	320	466	32	212	10.6	8.8	0.78	63%
37	THIRUMALAI	38	M	24	0.78	100/80	160	210	7.4	160	110	50	88	11	9.6	1.4	59%
38	VEDHACHALAM	48	M	30.24	0.98	136/78	230	360	10.4	200	150	40	110	12.6	9.8	0.82	69%
39	RAJAMANICKAM	43	M	20.77	1.06	100/68	128	189	6.6	224	168	55	136	11.4	8.1	1.4	65%
40	RAJANGAM	50	F	16.36	0.72	128/72	210	340	9.9	190	150	46	120	13	9.1	1.2	59%
41	MEENAMBAL	45	F	29.12	0.86	110/70	116	188	6.5	190	155	35	125	11.8	8.3	1.3	59%
42	RAJALAKSHMI	58	F	30.54	1.04	124/78	208	320	8.2	250	210	34	206	11.8	11	0.72	65%
43	SAVARIMUTHU	55	M	31.58	1.02	110/70	166	288	8.5	160	110	50	88	8.8	8.6	1.2	59%
44	VARALAXMI	40	F	22.35	0.72	134/80	188	310	9.1	190	160	40	128	11	9.5	1.1	60%
45	VASANTHA	45	F	26.26	0.81	110/70	126	244	7.4	175	120	46	90	10.2	7.9	1.2	68%
46	SHANMUGAM	44	M	22.41	0.86	124/78	166	310	8.9	194	138	44	110	9.6	8.3	1.3	62%
47	MUNIYANDI	51	M	21.93	1.24	100/70	210	298	9.2	224	322	30	152	11	8.1	1.2	59%
48	ALAMELU	45	F	33.29	1.1	110/82	152	290	8.4	192	210	32	118	11	12	0.76	60%
49	VALLI	45	F	24.56	0.86	136/78	155	208	7.4	256	336	36	148	8.5	7.4	1.4	64%
50	JAMES	45	M	20.8	0.78	120/80	126	188	6.7	170	120	46	100	8.8	9.6	1.3	60%

CONTROL GROUP

S.N	NAME	FBS	PPBS	BMI	WHR	BP	TC	TGL	HDL	LDL	IVS	LVPW	E/A	EF
1	SUMATHY 40/F	88	128	21.02	0.72	120/70	188	121	50	75.6	7.6	9.5	1.3	64%
2	LAKSHMI 46/F	100	127	24	0.85	130/82	154	100	48	68	8.2	9.7	1.2	59%
3	THAYANIDHI 50/M	96	121	23.12	0.79	140/88	190	176	51	104	8.6	7.1	1.1	55%
4	RAJAMANI 45/M	117	129	32	0.82	132/86	164	110	56	86	8.2	9.2	1.2	58%
5	PANDIAN 43/M	82	107	24.21	0.93	126/76	222	194	34	149	9.5	8.8	1.2	56%
6	KANDASAMY 51/M	110	126	20.14	0.81	110/70	180	156	55	93.8	9.7	9.6	1.4	60%
7	ANNAMANI 43/F	103	121	18.26	0.9	130/80	185	189	40	138	8.9	9.8	1.3	58%
8	DEVAKI 40/F	112	127	24	0.72	120/80	140	118	60	56	9.2	8.1	1.3	65%
9	KRISHNAN 42/M	88	112	23.44	0.86	134/86	136	96	62	54	7.8	9.1	1.4	62%
10	RAMADEVI 54/F	82	118	31.5	1.01	140/80	271	200	36	110	11	9.8	0.74	64%
11	MALLIGA 45/F	97	127	25.63	0.82	126/78	210	188	38	134	9.9	11	1.2	59%
12	PARAMESWARI 38/F	90	126	23.3	0.82	110/70	158	116	60	78	11.2	8.6	1.3	64%
13	VASUDEVAN 37/M	78	118	28.04	1.27	100/70	164	125	55	84	9.8	9.5	1.4	58%
14	KANNAPPAN 68/M	98	134	23.87	0.79	140/86	240	190	32	130	10.8	12	0.82	56%
15	UMAIYAL 62/F	115	136	18.74	0.76	134/78	130	120	56	68	7.8	8.3	1.3	64%
16	SATHYA 47/F	99	113	24.12	0.83	120/80	202	180	44	153	7.4	8.1	1.2	60%
17	SELVAMUTHU 44/M	108	127	20	0.78	124/82	175	160	54	89	8.9	8.5	1.3	62%
18	MEERABAI 55/F	115	126	24	0.79	110/70	128	100	55	52	9.2	7.4	1.3	64%
19	CHANDRAN 48/M	113	129	25.33	0.84	120/80	120	103	58	41	8.4	8.6	1.2	68%
20	POOVATHAA 52/F	107	127	24.5	0.9	140/90	146	130	50	70	11	8.2	0.8	61%
21	KAMALABAI 42/F	84	108	19.9	0.83	110/70	150	121	50	76	8.2	9.5	1.4	58%
22	ANJALAI 50/F	100	128	24.8	0.86	130/80	102	90	48	36	11	9.7	1.3	59%
23	ARUMUGAM 56/M	96	121	16.5	0.77	120/76	190	176	51	103	10	8.9	1.2	68%
24	KADHAR 49/M	82	107	20	0.78	132/76	222	195	34	149	9	9.2	1.3	61%
25	CHEZHIYAN 34/M	117	129	21	0.77	120/80	164	109	56	86	7.1	7.8	1.2	63%

CONTROL GROUP

S.N	NAME	FBS	PPBS	BMI	WHR	BP	TC	TGL	HDL	LDL	IVS	LVPW	E/A	EF
26	IRRUSAPPAN 70/M	70	118	17.14	0.93	130/80	196	138	38	100	9.2	11	1.3	60%
27	SURYA DEVI 54/F	115	136	21.05	0.7	124/78	210	168	40	120	8.8	9.9	1.3	64%
28	SHANMUGAVEL 62/M	99	113	18.73	0.76	140/86	190	134	46	100	9.6	11.2	0.75	59%
29	MANSRANI 40/F	108	127	20.77	0.76	134/78	210	148	43	110	9.8	9.8	1.3	65%
30	RAMASAMY 53/M	115	126	20	0.84	120/80	200	132	40	100	8.1	8.5	1.1	58%
31	RAJENDRAN 53/M	113	129	24.16	0.91	124/82	198	136	42	90	9.1	8.9	1.4	62%
32	PADMA 39/F	107	127	17.34	0.84	110/70	190	118	38	130	8.3	9.2	1.2	60%
33	YOGALAKSHMI 37/F	92	128	16.5	0.77	120/80	184	140	44	112	11	8.4	1.2	58%
34	SELVI 38/F	100	166	20.12	0.92	140/90	196	152	42	120	8.6	11	1.1	63%
35	MARIAMMAL 40/F	102	134	21.05	0.8	110/70	188	138	46	90	9.5	8.2	1.4	62%
36	DEVIKA 61/F	86	127	24.12	0.88	120/70	230	188	36	140	9.8	11	0.94	64%
37	MARIYAAL 34/F	98	133	23	0.76	130/82	190	144	42	110	8.3	10	1.2	59%
38	ABIRAMI 50/F	105	150	17.72	0.88	140/88	128	105	48	98	8.1	9	1.2	64%
39	CHAKKUBAI 50/F	78	108	22	0.85	132/86	188	143	56	100	8.5	7.1	1.1	58%
40	NATARAJAN 38/M	110	154	20.12	0.78	126/76	175	100	40	88	7.4	9.2	1.4	56%
41	LATHA 43/F	94	100	20.5	0.86	110/70	134	98	56	54	9.6	8.8	1.2	64%
42	ARUMUGAM 50/M	82	118	18	0.89	130/80	164	110	45	78	8.7	9.6	1.3	61%
43	VALLIAMMAL 46/F	97	127	24.21	0.8	120/80	220	188	34	130	9.8	9.8	1.3	62%
44	SUKUMAR 39/M	90	126	26	0.97	134/86	196	156	32	140	10.8	8.1	1.4	62%
45	RAJANGAM 40/F	78	118	19.12	0.86	140/80	180	134	42	100	7.2	7.6	1.2	61%
46	MEENAMBAL 42/F	98	134	21	0.7	126/78	188	121	50	75.6	9.6	8.2	1.3	60%
47	RAJALAKSHMI 40/F	115	136	23.23	0.79	110/70	154	100	48	68	8.1	8.6	1.3	64%
48	SAVARIMUTHU 55/M	99	113	21.18	0.85	122/86	190	176	51	104	9.8	8.2	1.4	67%
49	VARALAXMI 40/F	78	118	17.12	0.82	130/70	164	110	56	86	11	9.5	1.2	62%
50	VASANTHA 45/F	98	128	25	0.92	110/70	222	194	34	149	8.2	9.7	1.3	59%